# Subarachnoid Hemorrhage

By Sherry Hsiang-Yi Chou, MD, MSc, FNCS, FCCM

REVIEW ARTICLE

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## ABSTRACT

PURPOSE OF REVIEW: **Subarachnoid hemorrhage (SAH) remains an important cause of mortality and long-term morbidity. This article uses a case-based approach to guide readers through the fundamental epidemiology and pathogenesis of SAH, the approach to diagnosis and management, the results of clinical trials and evidence to date, prognostic considerations, controversies, recent developments, and future directions in SAH.**

RECENT FINDINGS: **Historically, management of SAH focused on prevention and treatment of subsequent cerebral vasospasm, which was thought to be the primary cause of delayed cerebral ischemia. Clinical and translational studies over the past decade, including several therapeutic phase 3 randomized clinical trials, suggest that the pathophysiology of SAH-associated brain injury is multiphasic and multifactorial beyond large vessel cerebral vasospasm. The quest to reduce SAH-associated brain injury and improve outcomes is shifting away from large vessel cerebral vasospasm to a new paradigm targeting multiple brain injury mechanisms, including early brain injury, delayed cerebral ischemia, microcirculatory dysfunction, spreading cortical depolarization, inflammation, and the brain-body interaction in vascular brain injury with critical illness.**

**Despite multiple negative randomized clinical trials in search of potential therapeutic agents ameliorating the downstream effects after SAH, the overall outcome of SAH has improved over recent decades, likely related to improvements in interventional options for ruptured cerebral aneurysms and in critical care management. Emerging clinical evidence also suggests potential harmful impact of historic empiric treatments for SAH-associated vasospasm, such as prophylactic induction of hypertension, hypervolemia, and hemodilution (triple H therapy).**

**With decreasing mortality, long-term SAH survivorship and efforts to reduce chronic morbidity and to improve quality of life and patient-centered outcome are growing areas of unmet need. Despite existing guidelines, significant variabilities in local and regional practices and in scientific terminologies have historically limited advancement in SAH care and therapeutic development. Large global collaborative efforts developed harmonized SAH common data elements in 2019, and studies are under way to examine how existing variabilities in SAH care impact long-term SAH outcomes.**

SUMMARY: **Although the overall incidence and mortality of SAH is decreasing with advances in preventive and acute care, SAH remains a major cause of**

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Dr Chou serves on the board of directors of the Neurocritical Care Society, on an advisory board for CSL Behring, and on the editorial board of *Stroke*. Dr Chou receives research/grant support from the National Institute of Neurological Diseases and Stroke (R21NS113037) and the National Institutes of Health/National Center for Advancing Translational Sciences (UL1 TR001857).

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**long-term morbidity in survivors. Significant variabilities in care settings and empiric treatment protocols and inconsistent scientific terminologies have limited advancement in patient care and therapeutic clinical studies. Large consensus efforts are under way to introduce clinical guidelines and common data elements to advance therapeutic approaches and improve patient outcome.**

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## INTRODUCTION

Acute bleeding into the subarachnoid space can have multiple etiologies (TABLE 2-1[1–3]), but by far the most common and most severe form is nontraumatic spontaneous subarachnoid hemorrhage (SAH). This article focuses on adults with nontraumatic SAH. SAH is rare in children, and the etiologies are different from those in the adult population. In children under 15 years of age, the most common cause of nontraumatic SAH is cerebral arteriovenous malformation.

SAH is the least common type of stroke (1% to 6% of all strokes). However, it disproportionately affects a younger population and leads to extensive long-term morbidity in addition to having higher mortality.[4,5] SAH is responsible for more than 27% of life-years lost before age 65 and leads to disproportionately high societal health care costs and economic impact.[4,6] In particular, aneurysmal SAH from the rupture of intracerebral aneurysms is the deadliest form of SAH, with a case-fatality rate up to 51% and long-term disability in one-third to one-half of all survivors. The most common cause of spontaneous SAH is a ruptured cerebral aneurysm (85%). Approximately 10% to 15% of patients with SAH do not have an identifiable bleeding source; of these, approximately 38% have nonaneurysmal perimesencephalic SAH, which is a benign variant of SAH with generally excellent prognosis.[1-3] The incidence of aneurysmal SAH is approximately 30,000 per year in the United States and 6.1 per 100,000 person-years worldwide,[7] with females affected 1.6 times more often than males.[8]

The American Heart Association (AHA)/American Stroke Association (ASA) SAH guidelines from 2012[5] and Neurocritical Care Society guidelines from 2011[9] are the most recent clinical guidelines for SAH management, with an updated iteration of guidelines by the Neurocritical Care Society currently under development.

## EPIDEMIOLOGY, RISK FACTORS, AND SCREENING

Although the primary risk of SAH comes from having an intracranial aneurysm, the incidence of unruptured intracranial aneurysms in the population far exceeds that of SAH[10]; only an estimated 0.3% of all unruptured intracranial aneurysms rupture per year, suggesting that not all unruptured intracranial aneurysms rupture and lead to SAH and that not all unruptured intracranial aneurysms may require acute intervention.[11,12] Data from a 2020 study suggest that patients with extracranial aneurysms have a higher prevalence of intracerebral aneurysms.[13]

Risk factors associated with rupture of an existing unruptured intracranial aneurysm may include hypertension, age, larger aneurysm, and aneurysm location and shape, whereas data on the impact of ethnic origin and family history are limited.[14-18] Aneurysms that are growing or causing clinical symptoms



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## Differential Diagnosis of Subarachnoid Hemorrhage in Adults

TABLE 2-1

### Primary subarachnoid hemorrhage (SAH)[1]

- **Aneurysmal SAH (85%): SAH due to rupture of intracerebral aneurysm**
- **Nonaneurysmal SAH (perimesencephalic SAH) (10%): SAH with no evidence of cerebral aneurysm or other vascular malformations**
- **SAH due to other vascular malformations (5%): SAH due to bleeding from cerebral or spinal arteriovenous malformation, dural arteriovenous fistula, arterial dissection, moyamoya disease, or other malformation**

### Secondary SAH etiologies[2]

- **Trauma**
- **Reversible cerebral vasoconstriction syndrome**
- **Posterior reversible encephalopathy syndrome (PRES)**
- **Cerebral amyloid angiopathy**
- **Pituitary apoplexy**
- **Cerebral vasculitis**
- **Primary intracerebral hemorrhage with secondary extension to subarachnoid space**
- **Cerebral venous sinus thrombosis**
- **Tumor/neoplasm**
- **Coagulopathy**
- **Sympathomimetic recreational drug use**
- **Heavy alcohol use**
- **Septic emboli to brain from endocarditis**
- **Iatrogenic injury to cerebral vasculature**

### Pseudo-SAH on imaging[3]

- **CT**
  - Anoxic brain injury
  - Spontaneous intracranial hypotension
  - Iatrogenic (eg, secondary to cerebral arterial thrombectomy)
- **Fluid-attenuated inversion recovery (FLAIR) MRI**
  - Supplemental oxygen
  - CSF pulsation
  - Contrast (gadolinium) leakage (eg, in broken blood-brain barrier or with renal failure)
  - Insufficient suppression, patient motion

CSF = cerebrospinal fluid; CT = computed tomography; MRI = magnetic resonance imaging.

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are generally referred for expeditious repair, although this has not been studied in a prospective clinical trial. For asymptomatic or nongrowing unruptured intracranial aneurysms, the preventive treatment strategy is less clear, as currently available aneurysm treatment modalities carry a 6% risk of complications resulting in permanent disability or death.[19,20] Generally, larger asymptomatic unruptured intracranial aneurysms are referred for neurosurgical or endovascular treatment because they are thought to be at higher risk for rupture, with the average size of a ruptured cerebral aneurysm being 6 mm to 7 mm.[21] However, because smaller unruptured intracranial aneurysms have much higher baseline population prevalence than larger unruptured intracranial aneurysms, small cerebral aneurysms account for most cases of SAH.[22] Currently, the multicenter PROTECT-U (Prospective Randomized Open-label Trial to Evaluate Risk faCTor Management in Patients With Unruptured Intracranial Aneurysms) trial is actively enrolling patients who do not qualify for preventive unruptured intracranial aneurysm interventions.[12] PROTECT-U examines the risk for aneurysm rupture or aneurysm growth in patients treated with 100 mg/d aspirin plus intensive systolic blood pressure control to less than 120 mm Hg compared to standard care.

The incidence of SAH increases with age and peaks in the fifth and sixth decades, is higher in females, and is more common in African American, Hispanic, Japanese, and Finnish populations.[1,4,5,14] The global incidence of SAH has fallen since 1998 by approximately 0.6% per year.[23] Genetically, approximately 10% of individuals with autosomal dominant polycystic kidney disease have asymptomatic unruptured intracranial aneurysms.[24] Autosomal dominant polycystic kidney disease accounts for 0.3% of all SAH cases.[25] Although familial clustering is seen in SAH, variabilities in genetic loci account for only 5% of the hereditary risk of SAH, suggesting that familial clustering may also be related to shared environmental risk factors. The risk in first-degree relatives of patients with SAH is 3 to 7 times higher than in the general population, but second-degree relatives have risks similar to that of the general population.[26] Although several genetic polymorphisms have been linked to higher risk for intracranial aneurysms, no predominant genetic risk factor has been identified for either unruptured cerebral aneurysm or for SAH. Currently, no clinical genetic screening tests are recommended for SAH or unruptured cerebral aneurysm risk determination.[27] Epidemiologic studies of familial clustering of cerebral aneurysms and SAH suggest that environmental factors may be more important than genetic factors in familial cases.[28] The International Study of Unruptured Intracranial Aneurysms found that people with two or more first-degree relatives with cerebral aneurysm or SAH are at increased risk for aneurysmal SAH, particularly when the affected probands are siblings.[17,29-31] Based on this, the AHA/ASA SAH guidelines suggest screening be considered in those with two or more first-degree relatives with aneurysm or SAH.[27]

Potentially modifiable risk factors for SAH include hypertension, smoking, heavy alcohol use, and sympathomimetic recreational drug (eg, cocaine) use.[32] Although no prospective clinical trials have proven that modifying these risk factors indeed lowers SAH risk, these preventive measures are generally recommended in clinical practice. Nonmodifiable SAH risk factors include age, female sex, family history, ethnicity/nation of origin, and a history of SAH.

Over the past 2 to 3 decades, the SAH case-fatality rate has decreased by 17% to 50% worldwide,[33] likely a result of multiple factors, including advances in



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stroke systems of care, diagnostic accuracy, surgical techniques, and critical care support. For many years, the global incidence of SAH did not change, and no preventive measures for SAH had been identified. However, a 2019 meta-analysis found a declining worldwide incidence for SAH, possibly because of cardiovascular risk prevention measures, such as hypertension control and smoking cessation.[7] Despite these advances, SAH remains a highly deadly and morbid disease, with 30-day mortality as high as 35%.[33,34] The overall mortality of SAH may be underestimated, as patients with SAH who are found dead or who die before hospital arrival may not receive the diagnosis.

## CLINICAL PRESENTATION AND DIAGNOSIS

Patients with SAH can present with a variety of symptoms and signs, including non-neurologic organ dysfunction (TABLE 2-2[35,36]). The classic SAH presentation is characterized by the sudden development of a severe headache, often referred to as thunderclap headache or the worst headache of life, which can be associated with nausea, vomiting, meningismus, altered mental status, loss of consciousness, seizure, or seizurelike events (CASE 2-1A), or in some cases patients may develop acute focal strokelike deficits associated with bleeding into intraparenchymal or subdural spaces.[37] Approximately 70% of patients with SAH present with sudden headache. A subset of patients with SAH may experience a sentinel headache that precedes SAH diagnosis by days to weeks. Although many suspect a sentinel headache represents a minor rupture of cerebral aneurysm before SAH, the pathophysiology and clinical significance of sentinel headaches are not yet fully understood.[38]

### What Headaches Suggest the Presence of Subarachnoid Hemorrhage?

Acute SAH constitutes approximately 1% to 4% of all emergency department visits for acute headaches.[39] The decision whether to pursue invasive diagnostics to rule out a rare but lethal headache etiology is often a diagnostic dilemma, particularly in patients with acute headache and no other neurologic symptoms. The Ottawa SAH Rule is a decision rule validated for use in the emergency department to screen for SAH in patients with acute headache who are neurologically intact (TABLE 2-3).[40,41] Implementation of the Ottawa SAH Rule in practice has reduced the total number of lumbar punctures done while retaining 100% sensitivity for SAH.

Delayed or missed diagnosis of aneurysmal SAH is common, particularly in patients in good clinical condition at presentation.[39,42] Incorrect or delayed diagnosis of aneurysmal SAH has profound consequences, leading to increased rates of aneurysm rebleeding, unfavorable outcome, and death.[43] Aneurysmal SAH from a ruptured cerebral aneurysm or other bleeding cerebral vascular malformation is a neurologic emergency that requires immediate diagnosis and rapid transfer to a high-volume center. The most common diagnostic error leading to missed or delayed diagnosis of aneurysmal SAH is the failure to obtain a head CT.[43]

### Subarachnoid Hemorrhage Clinical and Radiographic Severity Scores

The initial clinical severity of SAH presentation also varies from very mild to critical. SAH clinical severity is most commonly measured using the Hunt and Hess Scale[44] or the World Federation of Neurological Surgeons Scale (WFNSS),[45] or both (TABLE 2-4). The Hunt and Hess Scale and WFNSS were initially developed in 1968 and 1988 to predict surgical risk and mortality in SAH.

**KEY POINTS**

- Subarachnoid hemorrhage (SAH) is the least common type of stroke syndrome (1% to 6% of all strokes) but leads to significant morbidity and disproportionately high societal health care costs and economic impact.
- The incidence of SAH increases with age and peaks in the fifth and sixth decades; is higher in females; and is more common in African American, Hispanic, Japanese, and Finnish populations.
- Although familial clustering is seen in SAH, most cases of SAH are sporadic. People with two or more first-degree relatives with cerebral aneurysm or SAH are at increased risk for aneurysmal SAH. The American Heart Association/American Stroke Association guidelines recommend screening in those with two or more first-degree relatives with aneurysm or SAH.
- The classic SAH presentation is characterized by the sudden development of a severe headache, often referred to as the worst headache of life, which can be associated with nausea, vomiting, meningismus, altered mental status, loss of consciousness, seizure or seizurelike events, and acute focal strokelike deficits.

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Although surgical techniques and critical care management for SAH have advanced significantly since that time, epidemiologic studies consistently show that SAH clinical severity scores remain the strongest predictors of SAH functional outcome.[46] The best timing of WFNSS or Hunt and Hess Scale assessment has been a subject of debate, particularly as initial SAH presentations can be confounded by acute hydrocephalus or other potentially reversible conditions in which patients' neurologic functions improve following emergent resuscitative measures such as external ventricular drain (EVD) insertion. Recent data now suggest that a postresuscitation WFNSS is more predictive of final SAH outcome.[47,48]

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**TABLE 2-2** **Aneurysmal Subarachnoid Hemorrhage Presenting Symptoms and Signs**

**Symptoms**

- Worst headache of life: sudden onset of severe headache
- Sentinel headache: a new headache without other associated subarachnoid hemorrhage symptoms that is later followed by life-threatening aneurysm rebleeding, leading to diagnosis of aneurysmal subarachnoid hemorrhage (40%)[35]
- A change in headache characteristics: patients with a history of headaches may develop a new headache that is different in quality and severity from their baseline headache syndrome
- Nausea, often with vomiting
- Sudden loss of consciousness, transient syncope
- Acute onset or progressive altered mental status

**Neurologic examination findings**

- Altered mental status
- Abnormal Glasgow Coma Scale score
- Focal cranial nerve palsies and ophthalmoplegia (eg, third nerve palsy from posterior communicating artery aneurysm, sixth nerve palsy from increased intracranial pressure)
- Meningismus: neck stiffness, photophobia
- Terson syndrome: intraocular extension of subarachnoid blood[36]
- Acute hemiparesis or hemiplegia due to focal intracerebral hematoma from aneurysm rupture
- Bilateral leg weakness and abulia due to mass effect from hematoma in the interhemispheric fissure
- Seizure or seizurelike events
- Focal neurologic deficits

**Systemic manifestations**

- Acute hypertension
- Cardiac arrhythmia
- Cardiac arrest
- Hypotension/shock from neurogenic stunned myocardium
- Hypoxia from aspiration, respiratory depression, or neurogenic pulmonary edema



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Patients with SAH can also present with a broad range of radiologic bleeding severity, from a thin layer of subarachnoid blood to extensive and thick hematomas involving all basal cisterns with extension into the intraventricular, intracerebral, and, at times, subdural spaces. The Fisher Scale is an original SAH radiographic severity scale developed in the 1980s to predict the risk of delayed cerebral vasospasm.[49] Since then, additional scales have been developed that have better predictive value for subsequent vasospasm and where vasospasm risks consistently increase with incremental increase in radiologic severity score, which was not the case with the original Fisher Scale. Currently, the most commonly used radiographic SAH severity scores are the modified Fisher Scale[50] and the Hijdra Scale[51] (TABLE 2-5).

### Diagnostic Imaging

Noncontrast head CT is the most common modality that identifies the presence of acute blood in the subarachnoid space. TABLE 2-6 summarizes key characteristic appearance features of aneurysmal SAH on head CT. Of patients with classic CT findings for aneurysmal SAH, 85% have a ruptured cerebral aneurysm, 5% have other cerebrovascular malformations, and 10% have no cerebrovascular malformations identified and are classified as having nonaneurysmal or perimesencephalic SAH. Other secondary etiologies of SAH include trauma, reversible cerebral vasoconstriction syndrome, cerebral amyloid angiopathy, vasculitis, cerebral venous sinus thrombosis, or bleeding into the subarachnoid space because of systemic conditions (such as coagulopathy), infectious conditions (such as septic brain emboli from endocarditis), or toxic-metabolic etiologies (such as cocaine use) (TABLE 2-1). Secondary SAH has different CT characteristics and tends to be present in the high cerebral convexity and not centered around the basal cisterns as in aneurysmal SAH.[2,3]

Head CT is the go-to modality because of ease of access and rapidity of diagnostic results. It is most sensitive for SAH in the first 6 to 12 hours following aneurysm rupture, with a sensitivity of 93% to 100%. Diagnostic sensitivity by head CT degrades over time, declining to 60% at 7 days post-SAH.[52] In the first 6 hours of SAH, MRI may be slightly superior to head CT in detecting the presence of SAH.[52] For subacute or chronic phases of SAH, MRI with gradient recalled echo (GRE), susceptibility-weighted imaging (SWI), or fluid-attenuated inversion recovery (FLAIR) sequences have superior sensitivity compared to noncontrast head CT.[53]

### Lumbar Puncture and CSF Analysis

In cases of negative or equivocal imaging and high clinical suspicion for SAH, lumbar puncture for diagnostic CSF analysis can assist in the diagnosis of acute SAH, although the value of lumbar puncture has been questioned.[54] The classic diagnostic criterion is presence of xanthochromia on laboratory spectrophotometry analysis. It is important to note that xanthochromia, particularly if evaluated visually and not by spectrophotometry, may not be apparent in the hyperacute phase of SAH. In addition to CSF analysis, lumbar puncture offers the opportunity to measure an opening pressure as a surrogate for intracranial pressure (ICP). It is recommended that a closing pressure be measured after CSF sampling through a lumbar puncture, particularly if the opening pressure is abnormal.

**KEY POINTS**

- SAH is a neurologic emergency that requires immediate diagnosis and rapid transfer to a high-volume center. Delayed or missed diagnosis of SAH is common and often associated with severe consequences, including death and severe morbidity. The most common diagnostic error leading to missed or delayed diagnosis of SAH is the failure to obtain a head CT scan.
- Diagnostic head CT is most sensitive for SAH in the first 6 to 12 hours following aneurysm rupture. For subacute or chronic phases of SAH, MRI with gradient recalled echo, susceptibility-weighted imaging, or fluid-attenuated inversion recovery sequences has superior sensitivity compared to noncontrast head CT.
- In cases of negative or equivocal imaging and high clinical suspicion for SAH, lumbar puncture to evaluate for CSF xanthochromia is recommended.
- After initial resuscitation and stabilization of a patient with SAH, a key next step is to rapidly identify and secure the bleeding source to minimize the risk for aneurysm rerupture. Cerebral CT angiography is often the first-line imaging modality, with 90% to 97% sensitivity in detecting an intracranial aneurysm. Digital subtraction angiography with three-dimensional reconstructions remains the gold standard diagnostic modality for cerebral aneurysms.

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## CASE 2-1A

A 46-year-old woman suddenly collapsed with jerking movements and vomiting. She was brought to the emergency department 30 minutes later. The patient was in good health except for high blood pressure and cigarette smoking. She took no medications, had no history of recreational drug use, and had never had seizures before. On arrival at the emergency department, she was urgently intubated and given a 2000 mg IV levetiracetam load. Emergent head CT (FIGURE 2-1) demonstrated diffuse subarachnoid hemorrhage (SAH). She was emergently transferred to a comprehensive stroke center. Before transfer, she had intact brainstem reflexes and was spontaneously moving all limbs.

On arrival at the comprehensive stroke center, her heart rate was 105 beats/min in sinus rhythm. Her blood pressure was 180/110 mm Hg, and her temperature was 38 °C (100.4 °F). She was intubated, and oxygen saturation was 98% on 100% $FIO_2$. Urine pregnancy test was negative, and finger stick glucose was 110 mg/dL. On train-of-four testing (peripheral nerve stimulator test for depth of neuromuscular blockade), she had 4/4 twitches, suggesting no residual effect of the pharmacologic paralytic agent. On examination, the patient was in a cervical spine immobilization collar. After her propofol drip was stopped for 20 minutes, she remained obtunded. She grimaced symmetrically and slowly withdrew all four extremities to deep noxious stimuli. Her pupils were 5 mm, equal, and reactive. When her eyes were held open, she had forced downward gaze. Corneal, cough, and gag responses were present but diminished. She had bilateral spontaneously upgoing toes, hyperactive deep tendon reflexes without clonus, and increased tone in bilateral lower extremities.

Emergent CT head demonstrated acute obstructive hydrocephalus with dilated temporal horns of the lateral ventricle, dilated third ventricle, acute blood in the distal cerebral aqueduct and fourth ventricle, and evidence of transependymal CSF flow (FIGURE 2-2).

An external ventricular drain (EVD) for acute obstructive hydrocephalus was emergently placed. Upon insertion, the patient had an elevated CSF opening pressure of greater than 25 cm $H_2O$. CSF was slowly drained through an open EVD set at 20 mm Hg above the midbrain,

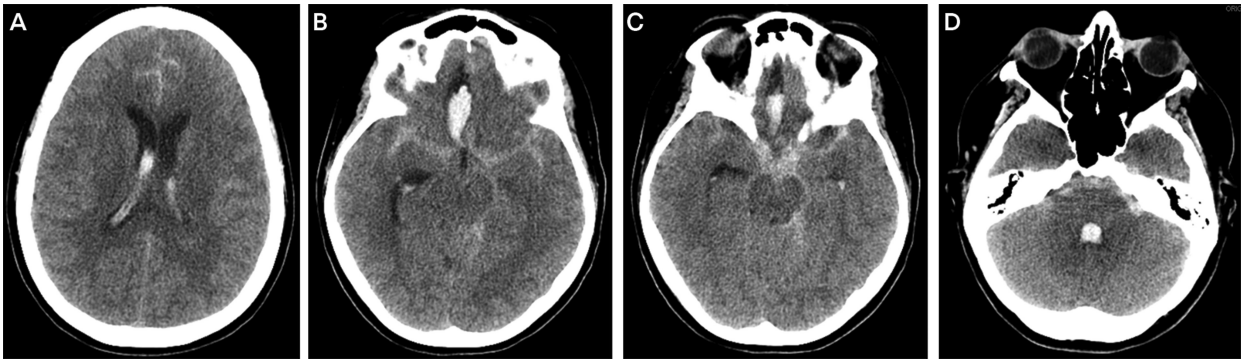


**FIGURE 2-1**
Initial imaging of the patient in CASE 2-1A. Axial noncontrast head CT shows acute subarachnoid hemorrhage with intraventricular extension (*A*), with focal clot in the interhemispheric fissure (*B*), perimesencephalic cistern (*C*), and fourth ventricle (*D*).



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after which the patient's intracranial pressure (ICP) returned to 18 mm Hg. The EVD was clamped for continuous ICP monitoring and only opened for ICP greater than 20 mm Hg. Acute hypertension was treated with a continuous IV labetalol drip titrated to maintain systolic blood pressure at less than 140 mm Hg to minimize the risk for cerebral aneurysm rerupture.

Follow-up CT demonstrated reduced acute hydrocephalus, and CT angiography suggested the presence of an anterior communicating artery cerebral aneurysm. The patient was then taken for urgent digital subtraction angiography, which confirmed the presence of an anterior communicating artery cerebral aneurysm with intramural thrombosis (FIGURES 2-3). The aneurysm was successfully coil embolized (FIGURES 2-4).

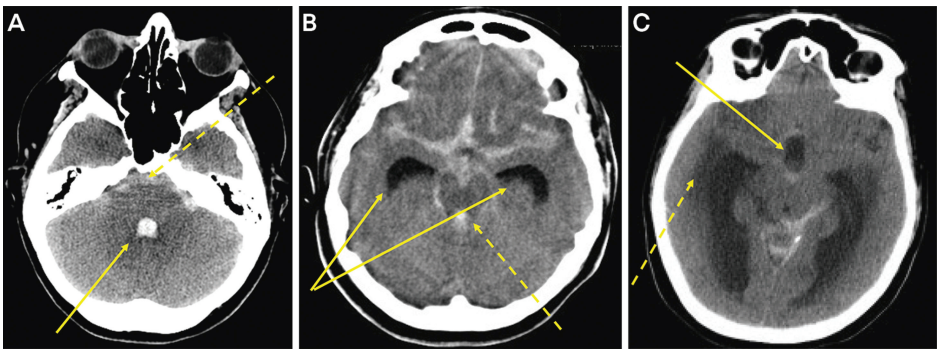


**FIGURE 2-2**

**Follow-up imaging of the patient in CASE 2-1A. Axial noncontrast head CT shows the presence of basilar subarachnoid blood with dense clot filling the fourth ventricle (*A*, *solid arrow* points to the fourth ventricular clot, *dotted arrow* points to the prepontine subarachnoid hemorrhage). Compared with initial imaging, the patient now has dilated temporal horns of the lateral ventricles (*B*, *C*, *solid arrows* in *B* point to temporal horns) with evidence of transependymal CSF flow (*C*, *dotted arrow*), dilated third ventricle (*C*, *solid arrow*), and acute clot in the cerebral aqueduct (*B*, *dotted arrow*).**

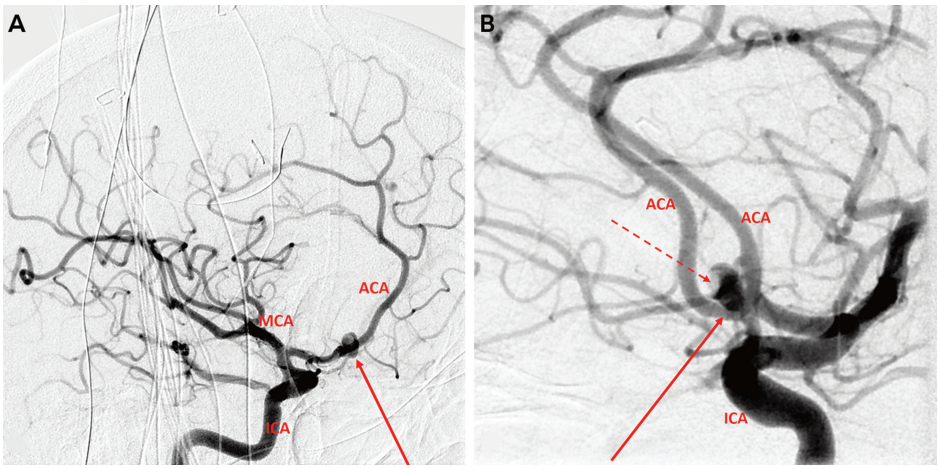


**FIGURE 2-3**

**Imaging of the patient in CASE 2-1A. Digital subtraction angiography lateral (*A*) and magnified transorbital oblique views (*B*) with internal carotid artery (ICA) contrast injection demonstrate the presence of an anterior communicating artery cerebral aneurysm (*A*, *B*, *solid arrow*) with partial intramural thrombosis (*dotted arrow*).**

ACA = anterior cerebral artery; MCA = middle cerebral artery.

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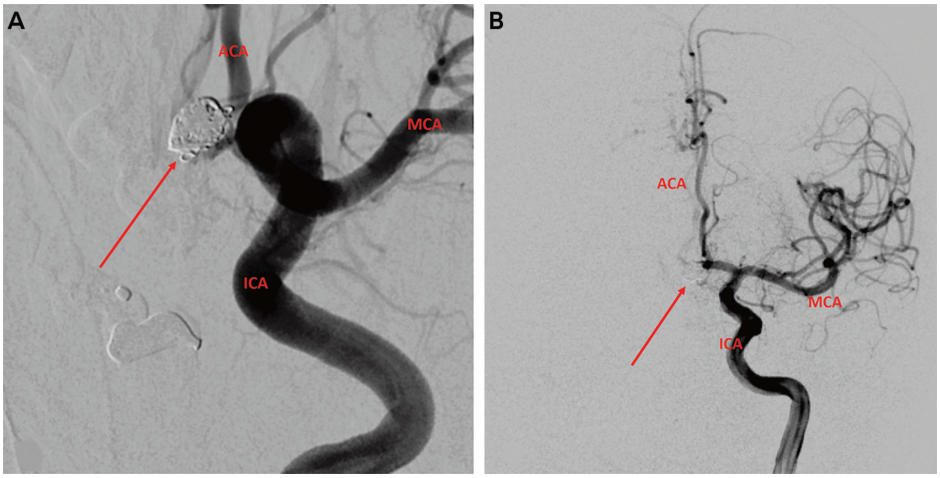


**FIGURE 2-4**

**Imaging of the patient in CASE 2-1A. Successful endovascular coil embolization of the anterior communicating artery cerebral aneurysm (*A*) in magnified transorbital oblique view with internal carotid artery (ICA) contrast injection, with no further contrast filling in the coiled aneurysm (*solid arrow*) on frontal view cerebral angiography with ICA contrast injection (*B*).**

ACA = anterior cerebral artery; MCA = middle cerebral artery.

**COMMENT**

This case illustrates the classic hyperacute clinical presentation, initial triage, differential diagnosis, and emergent treatment of acute aneurysmal SAH, including the prehospital phase. The initial presentation of aneurysmal SAH can often mimic seizure, acute stroke, trauma from fall/collapse, or cardiopulmonary emergencies and can easily be misdiagnosed. Life-threatening hyperacute complications from this phase of SAH include acute hydrocephalus, aneurysm rerupture, and SAH-associated acute extra-central nervous system organ dysfunctions, such as acute respiratory failure. Early and accurate diagnosis of aneurysmal SAH and emergent transfer to a high-volume center with neurosurgical, endovascular, and neurocritical care support can improve the patient's chances for survival and favorable outcome.

### Vessel Imaging to Identify Source of Bleeding

Once a patient is identified as having clinical and radiographic findings suggestive of aneurysmal SAH and following acute stabilization of airway, breathing, and spontaneous circulation as well as intracranial pressure, acute hydrocephalus, or mass effect on the brain, a key next step is to rapidly identify and secure the bleeding source. For those without contraindications, cerebral CT angiography (CTA) is often the first-line vessel imaging modality because it can be rapidly obtained together with the initial hyperacute diagnostic head CT. Cerebral CTA has 90% to 97% sensitivity in detecting an intracranial aneurysm compared to digital subtraction angiography (DSA) with three-dimensional reconstructions, which remains the gold standard diagnostic



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modality for cerebral aneurysms. A negative CTA is insufficient to rule out the presence of a bleeding aneurysm in patients with aneurysmal SAH, particularly when the bleeding aneurysm is smaller than 4 mm.[55] When cerebral aneurysms are detected on CTA, patients often still proceed to DSA, which is also a potential therapeutic modality for endovascular treatment of the bleeding aneurysm.

### Perimesencephalic Subarachnoid Hemorrhage

Patients with no aneurysms found on DSA with three-dimensional reconstructions are often referred to as having "angio-negative" SAH. A large proportion of these patients may have a CT pattern of perimesencephalic SAH, in which the presence of subarachnoid blood is isolated to the perimesencephalic or prepontine cisterns and no vascular malformations are found on DSA or other diagnostics. The population incidence of perimesencephalic SAH is approximately 0.5 per 100,000 person-years. This is thought to be a nonaneurysmal benign variant of primary SAH for which prognosis is generally excellent (CASE 2-2).[56,57] Unlike aneurysmal SAH, perimesencephalic SAH affects men more often than women.[58] Approximately 10% of perimesencephalic pattern SAHs are due to rupture of posterior circulation aneurysms. For perimesencephalic pattern SAH, cerebral CTA and three-dimensional DSA have similar sensitivity in detecting an aneurysm, and whether DSA is needed following a negative CTA remains controversial.

Of patients with a classic aneurysmal pattern of bleed on CT and negative initial DSA, between 4% and 25% may later be diagnosed with a vascular malformation on repeat DSA or develop life-threatening rebleeding.[56,59] A repeat DSA days to weeks later can detect an aneurysm in 7% to 14% of these patients.[60] Many centers will perform repeat DSA in patients with SAH with negative initial DSA to minimize the risk of missing an acute bleeding source. Overall, approximately 15% of patients with primary SAH do not have a bleeding source identified on imaging.[61] FIGURE 2-6 summarizes a clinical algorithm for the acute diagnosis and evaluation of SAH.

**The Ottawa Subarachnoid Hemorrhage Rule**[a,b] TABLE 2-3

**Investigate if one or more high-risk variables present:**

- Age ≥40 years
- Neck pain or stiffness
- Witnessed loss of consciousness
- Onset during exertion
- Thunderclap headache (reaching maximum intensity within 1 minute of onset)
- Limited neck flexion on examination

[a] Data from Perry JJ, et al, CMAJ.[40]
[b] The Ottawa Subarachnoid Hemorrhage Rule applies to patients older than 15 years of age with new severe nontraumatic headache reaching maximum intensity within 1 hour.



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## HYPERACUTE STABILIZATION AND MANAGEMENT CONSIDERATIONS

Hyperacute life-threatening complications that can occur shortly after initial aneurysm bleeding include acute cardiopulmonary failure,[62-65] acute hydrocephalus, diffuse cerebral edema[66,67] and aneurysm rebleeding.[68,69] These events may occur in the prehospital phase, during initial evaluation and treatment in the emergency department, during acute interhospital transfer, or shortly after admission to the ICU. Acute symptomatic hydrocephalus can develop within minutes to days of aneurysm rupture and occurs in 20% of patients with SAH. Timely insertion of an external ventricular catheter for acute symptomatic hydrocephalus is lifesaving. TABLE 2-7[70] summarizes possible etiologies and clinical features of these hyperacute life-threatening events with aneurysmal SAH and resuscitative options.

### Cardiopulmonary Dysfunction and Cardiac Arrest With Aneurysmal Subarachnoid Hemorrhage

Patients with aneurysmal SAH can present in extremis, including presenting in cardiopulmonary arrest,[62-65] or may present with milder initial symptoms but then acutely deteriorate, often because of aneurysm rerupture or acute hydrocephalus. It is important to recognize aneurysmal SAH as a potential etiology in patients presenting with cardiac arrest, as delayed diagnosis is associated with high mortality. Although patients who present in cardiac arrest from aneurysmal SAH often have poor-grade SAH and high associated mortality and morbidity, a large 2020 multicenter cohort study showed good outcome is possible, and up to 25% patients with aneurysmal SAH who survived cardiac arrest were discharged to home after index aneurysmal SAH admission.[64]

Within the first week of SAH, acute left ventricular dysfunction is observed in up to 30% of patients, in whom severe cases can lead to significant reduction in ejection fraction and cardiogenic shock.[71] This phenomenon, often referred to as *neurogenic myocardial stunning* or *stress cardiomyopathy*, is thought to be secondary to the sudden catecholamine surge following cerebral aneurysm rupture, leading

**TABLE 2-4** Commonly Used Subarachnoid Hemorrhage Clinical Severity Grading Scales

| Grade | Hunt and Hess Scale[44] | World Federation of Neurological Surgeons Scale[45] |
|---|---|---|
| 1 | Asymptomatic or mild headache, minimal or no nuchal rigidity | Glasgow Coma Scale (GCS) score of 15, motor deficit absent |
| 2 | Moderate to severe headache, nuchal rigidity, and no neurologic deficit other than cranial nerve palsy | GCS score of 13-14, motor deficit absent |
| 3 | Mild alteration in mental status (confusion, lethargy), with or without mild focal neurologic deficit | GCS score of 13-14, motor deficit present |
| 4 | Stupor and/or hemiparesis | GCS score of 7-12, motor deficit absent or present |
| 5 | Comatose and/or decerebrate rigidity and/or no motor response | GCS score of 3-6, motor deficit absent or present |



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## Commonly Used Subarachnoid Hemorrhage Radiologic Severity Grading Scales

TABLE 2-5

| Grade | Fisher Scale[49] | Modified Fisher Scale[50] | Hijdra Scale[51,a] |
|---|---|---|---|
| **0** | NA | No subarachnoid hemorrhage (SAH) or intraventricular hemorrhage (IVH) | No blood in the cistern or ventricle |
| **1** | No SAH or IVH | Localized or diffuse thin SAH, with no IVH | Small amount of blood in cistern, sedimentation of blood in the posterior part of ventricle |
| **2** | Diffuse deposition of thin layers of subarachnoid blood with vertical layers of blood (interhemispheric fissure, insular cistern, ambient cistern) <1 mm thick | Localized or diffuse thin SAH, with IVH | Moderate amount of blood in cistern, ventricle partly filled with blood |
| **3** | Vertical layers of blood (interhemispheric fissure, insular cistern, ambient cistern) ≥1 mm thick or localized clots (defined as >3 × 5 mm) | Localized or diffuse thick SAH, with no IVH | Cistern completely filled with blood, ventricle completely filled with blood |
| **4** | Intracerebral or intraventricular clots with diffuse SAH or no subarachnoid blood | Localized or diffuse thick SAH, with IVH | NA |

NA = not applicable.
[a] Hijdra Scale grades each of the 10 cisterns and each of the four ventricles.

## Characteristic CT Appearance of Aneurysmal Subarachnoid Hemorrhage

TABLE 2-6

| CT features | Aneurysm locations |
|---|---|
| **Preponderance of subarachnoid blood in the basal cisterns** | All |
| **Subarachnoid blood along the sylvian fissure** | More common with middle cerebral artery aneurysms |
| **Subarachnoid blood in the interhemispheric fissure** | More common with anterior communicating artery or anterior cerebral artery aneurysms |
| **Subarachnoid blood in the interpeduncular cistern** | All |
| **Subarachnoid blood in prepontine area, fourth ventricular outlet, and foramen magnum** | Posterior circulation aneurysms |
| **Focal anterior temporal lobe intracerebral hematoma** | More common with middle cerebral artery aneurysms |
| **Focal frontal lobe intracerebral hematoma** | More common with anterior communicating artery or anterior cerebral artery aneurysms |
| **Concomitant subdural hematoma without associated head trauma** | A less typical presentation of aneurysmal subarachnoid hemorrhage |
| **Focal subarachnoid blood in the prepontine area** | Perimesencephalic subarachnoid hemorrhage with no cerebrovascular malformations identified |

CT = computed tomography.



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## CASE 2-2

A 55-year-old man with a history of type 2 diabetes and chronic back pain presented to the emergency department after developing a sudden severe headache originating from the posterior neck and radiating to the top of his head. His headache was much improved by the time he arrived at the emergency department. He had no other neurologic symptoms. His neck had been manipulated by a chiropractor earlier in the day. The patient had no history of alcohol or tobacco use. He took metformin daily and naproxen occasionally for pain.

On examination, his temperature was 36.2 °C (97.2 °F), blood pressure was 154/87 mm Hg, heart rate was 81 beats/min, respiratory rate was 22 respirations/minute, and arterial blood oxygen saturation was 98% on room air. He was alert and oriented. Cranial nerves, sensation, and strength were all intact. His laboratory values were within normal parameters except for glucose of 298 mg/dL. Urine toxicology screen was negative.

Emergent head CT without IV contrast demonstrated acute subarachnoid hemorrhage (SAH) in the premedullary, prepontine, and perimesencephalic cisterns (FIGURES 2-5A through 2-5C). Subarachnoid blood further extended into the suprasellar, sylvian, and the quadrigeminal cisterns (FIGURE 2-5D), which is atypical for benign nonaneurysmal SAH. CT angiography was not performed because the patient had a contrast allergy. After adequate premedication, the patient underwent diagnostic digital subtraction angiography (DSA) with three-dimensional reconstruction, on which no cerebrovascular abnormalities were detected. Specifically, no intracranial aneurysm or vertebral artery dissection was seen.

The patient was admitted to the neurocritical care unit and started on a clevidipine drip to target systolic blood pressure of less than 140 mm Hg to minimize the risk for rebleeding. He was monitored with neurologic checks every 2 hours, started on nimodipine 60 mg orally every 4 hours for prevention of delayed cerebral ischemia, and underwent daily transcranial Doppler ultrasound to monitor for cerebral vasospasm. He underwent MRI of brain and cervical spine and MR angiography (MRA) of the head and neck to evaluate for the presence of occult vascular abnormalities. Other than mild disk degeneration, facet hypertrophy, and foraminal stenosis, MRI and MRA detected no abnormalities.

The patient remained in the neurocritical care unit under close monitoring for the next 7 days. He remained neurologically intact except for headache and neck pain treated with oral acetaminophen. He remained on an IV clevidipine drip intermittently for hypertension control and required insulin for control of hyperglycemia. The patient underwent repeat DSA on postbleed day 7 after adequate premedication for contrast allergy. Once again, no cerebral aneurysm or other vascular abnormalities were detected. Strict blood pressure control to a systolic blood pressure less than 140 mm Hg with continuous IV antihypertensive medication was no longer indicated, and he was weaned off clevidipine. He remained stable and was discharged to home the next day.

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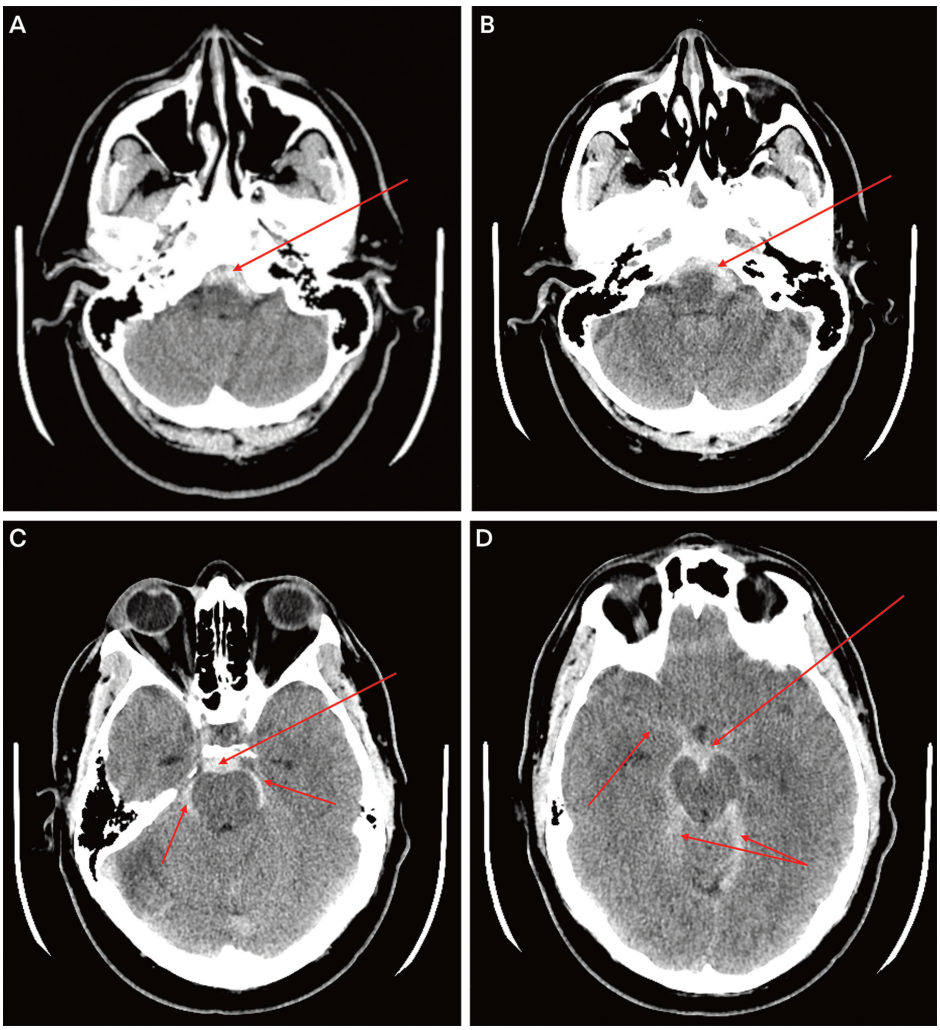


**FIGURE 2-5**

**Imaging of the patient in CASE 2-2. Axial noncontrast head CT shows acute subarachnoid hemorrhage in the premedullary (*A*), prepontine (*B*), and perimesencephalic cisterns (*C*). Higher and more diffuse subarachnoid blood extension to the suprasellar and sylvian cisterns and posterior extension in the quadrigeminal cistern (*D*) is an atypical feature for classic benign subarachnoid hemorrhage and raises concern for a possible underlying vascular malformation. *Red arrows* point to the acute blood clot in the subarachnoid space.**

**COMMENT**

This case illustrates the presentation and relatively benign clinical course of nonaneurysmal SAH. In addition to the classic CT appearance of perimesencephalic SAH, this patient had some atypical CT features concerning for a possible underlying aneurysmal source for the bleed. Although most nonaneurysmal SAHs have a benign clinical course, in atypical cases, patients can develop delayed cerebral vasospasm, delayed hydrocephalus, or even rebleeding from an occult cerebral aneurysm not visualized on the initial DSA. A common practice is to closely monitor these patients in a neurocritical care setting for these rare complications for several days and to perform a second DSA to confirm the absence of cerebral vascular malformation.



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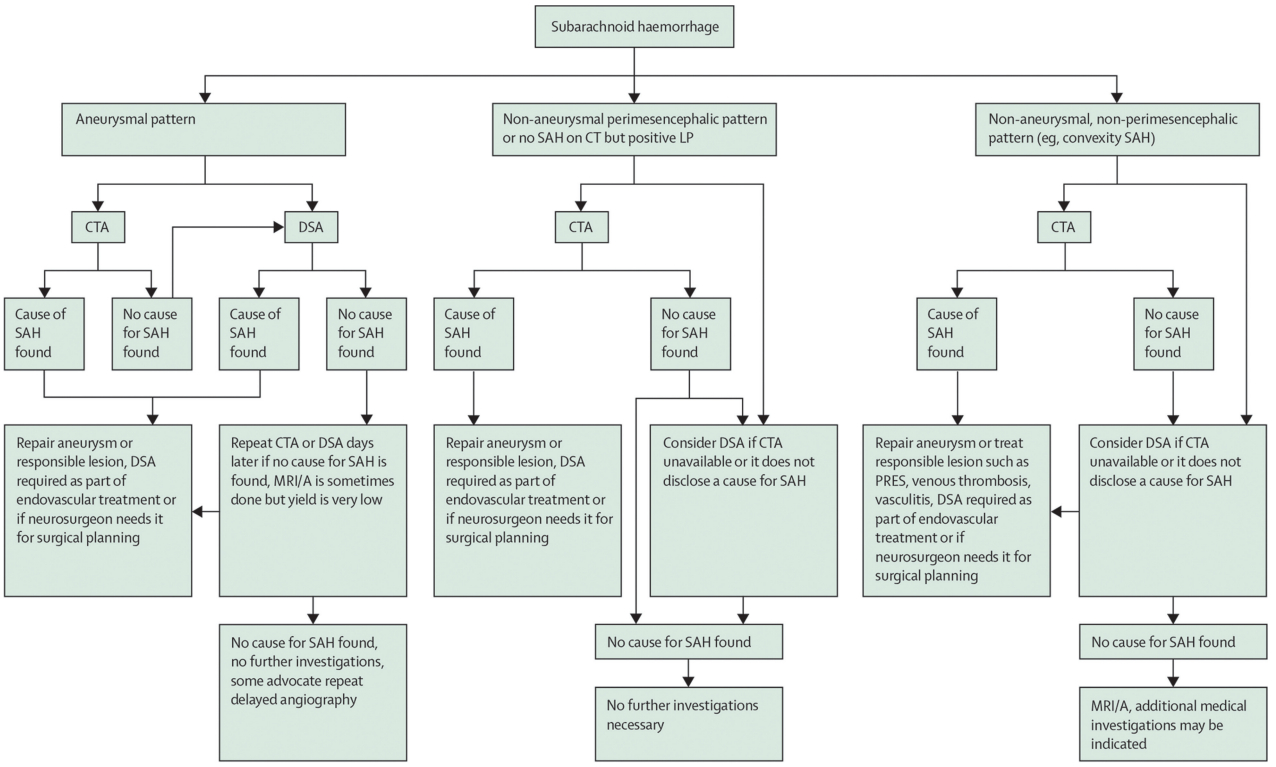
Subarachnoid haemorrhage
Aneurysmal pattern
Non-aneurysmal perimesencephalic pattern or no SAH on CT but positive LP
Non-aneurysmal, non-perimesencephalic pattern (eg, convexity SAH)
CTA
DSA
CTA
CTA
Cause of SAH found
No cause for SAH found
Cause of SAH found
No cause for SAH found
Cause of SAH found
No cause for SAH found
Cause of SAH found
No cause for SAH found
Repair aneurysm or responsible lesion, DSA required as part of endovascular treatment or if neurosurgeon needs it for surgical planning
Repeat CTA or DSA days later if no cause for SAH is found, MRI/A is sometimes done but yield is very low
Repair aneurysm or responsible lesion, DSA required as part of endovascular treatment or if neurosurgeon needs it for surgical planning
Consider DSA if CTA unavailable or it does not disclose a cause for SAH
Repair aneurysm or treat responsible lesion such as PRES, venous thrombosis, vasculitis, DSA required as part of endovascular treatment or if neurosurgeon needs it for surgical planning
Consider DSA if CTA unavailable or it does not disclose a cause for SAH
No cause for SAH found, no further investigations, some advocate repeat delayed angiography
No cause for SAH found
No further investigations necessary
No cause for SAH found
MRI/A, additional medical investigations may be indicated

**FIGURE 2-6**
**Algorithm for subarachnoid hemorrhage (SAH) investigation.**
CTA = computed tomography angiography; DSA = digital subtraction angiography; LP = lumbar puncture; MRI/A = magnetic resonance imaging/angiography; PRES = posterior reversible encephalopathy syndrome. Reprinted with permission from MacDonald RL, Schweizer TA, Lancet.[1] © 2016 Elsevier Ltd.

to myocardial cell contraction band necrosis.[72,73] Echocardiography may show diffuse or cardiac regional wall motion abnormality/hypokinesis with systolic dysfunction. A classic appearance of neurogenic stunned myocardium is left ventricle apical akinesis leading to ballooning of the apex during systole, often referred to as *takotsubo cardiomyopathy* as the left ventricular shape resembles that of a Japanese octopus trap (**CASE 2-3**). With appropriate critical care support, the myocardial stunning often improves over days to weeks, with recovery of left ventricular systolic function.

On ECG, patients often have QTc prolongation followed by T-wave abnormalities, and some will eventually develop a deeply inverted T wave, often referred to as *cerebral T wave*. Troponin elevation is common and seen in up to 30% of patients with SAH. Timely diagnosis and treatment of neurogenic myocardial stunning is important as the reduced cardiac output can directly affect cerebral perfusion, and patients are at increased risk for cardiac arrhythmias, including malignant rhythms such as ventricular tachycardia and fibrillation, which may lead to secondary insults to the acutely injured brain. The presence of QTc prolongation, troponin elevation, and neurogenic stunned myocardium have all been shown to predict unfavorable SAH outcomes.[74]

Acute pulmonary dysfunction and hypoxic respiratory insufficiency are common after SAH and have multiple etiologies, including respiratory depression and poor airway protection because of coma or altered consciousness, lung injury



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## Hyperacute Life-threatening Complications of Aneurysmal Subarachnoid Hemorrhage and Management Considerations

TABLE 2-7

| Clinical condition | Etiology and clinical features | Hyperacute management |
|---|---|---|
| **Respiratory insufficiency**[62,63] | Inability to protect airway because of coma/obtundation from acute intracranial pressure (ICP) elevation, hematoma mass effect, diffuse cerebral edema, hydrocephalus, or seizure<br><br>Acute aspiration from vomiting and altered mental status from acute subarachnoid hemorrhage (SAH)<br><br>Hypoxia from neurogenic pulmonary edema | Assess adequacy of airway, breathing, oxygenation, and ventilation<br><br>If clinically indicated, intubate and initiate mechanical ventilation<br><br>For nonintubated patients: close monitoring for delayed onset respiratory failure |
| **Hemodynamic instability, including presenting in cardiac arrest**[64,65] | Acute hypertension secondary to SAH-associated sympathetic surge and high ICP<br><br>Acute neurogenic cardiac arrhythmia and/or cardiac arrest<br><br>Reduced cardiac output and/or cardiogenic shock secondary to neurogenic stunned myocardium | Assess adequacy of systemic circulation and tissue perfusion In patients presenting in cardiac arrest or shock, resuscitate to establish return of spontaneous circulation<br><br>Consider and treat neurogenic causes for shock and cardiac arrhythmia in acute hemodynamic resuscitation |
| **Acute hydrocephalus**[70] | Acute blood in the subarachnoid space and/or intraventricular hemorrhage extension can lead to acute obstructive hydrocephalus<br><br>Symptoms of acute hydrocephalus include decreasing levels of consciousness, impaired upgaze, sixth nerve palsies; end-stage symptoms include respiratory depression, bradycardia, and hypertension (the Cushing response) | Emergent CSF diversion by inserting external ventricular drain can be lifesaving; in cases in which the CSF space is compartmentalized because of hematoma obstruction, more than one external ventricular drain may be necessary to adequately alleviate acute hydrocephalus |
| **Aneurysm rebleeding** | Rebleeding from ruptured cerebral aneurysm is often lethal, with associated mortality rate up to 60%<br><br>Highest rebleeding risk is within first 72 hours of aneurysm rupture (up to 23%); after the first month, rebleeding risk drops down to 3% per year<br><br>Risk factors include poor-grade SAH, hypertension, large aneurysm, and possibly the use of antiplatelet agents | Tightly control blood pressure and avoid extreme blood pressure peaks; guideline recommendations are to keep systolic blood pressure <160 mm Hg; practice variations exist, and many centers may target a lower blood pressure threshold in patients with a ruptured and unsecured cerebral aneurysm<br><br>Timely obliteration of bleeding aneurysm[a]<br><br>Short-term use of antifibrinolytic drug (ε-aminocaproic acid) may be safe but does not reduce rebleeding rate; prolonged use (>72 hours) is associated with increased thrombotic complications |
| **Global cerebral edema and ICP elevation**[66,67] | Acute global cerebral edema on SAH presentation occurs in 8-29% of patients and is associated with mortality and poor outcome | Presence of global cerebral edema may lead to ICP elevation and abnormal cerebral perfusion and metabolism.<br><br>No clinical trial data exist to guide management specifically in SAH; consider osmotic therapy to reduce edema and normalize ICP; a cerebral perfusion pressure–driven or other multimodal monitoring goal-directed management protocol for diffuse cerebral edema is reasonable |

CSF = cerebrospinal fluid.
[a] See TABLE 2-10 for further guideline recommendations from the American Heart Association/American Stroke Association and the Neurocritical Care Society.



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## CASE 2-3

A 70-year-old woman with a history of hypertension and smoking was found unresponsive in a bathroom. Emergency medical services found her obtunded with minimal respiratory effort and a weak pulse; she was emergently intubated and brought to the emergency department.

On arrival, her blood pressure was 75/50 mm Hg, her temperature was 36.8 °C (98.2 °F), and her heart rate was 110 beats/min with intermittent premature ventricular contractions. Finger stick glucose was 220 mg/dL. Urine toxicology screen was negative. Her extremities were cold and clammy. Her oxygen saturation was 92% on 80% $FIO_2$. Significant laboratory values included elevated creatinine at 2.1 mg/dL, elevated blood lactate of 3.5 mmol/L, elevated cardiac troponin at 5.5 ng/mL, and leukocytosis at 17,000 cells/$mm^3$. ECG showed QTc prolongation and T-wave inversion without active ischemic changes. Bedside ultrasound showed significantly reduced left ventricular contractility with apical akinesis and ballooning consistent with takotsubo cardiomyopathy. Lung ultrasound showed pulmonary edema. An emergent central venous catheter was inserted, and norepinephrine infusion was started to maintain a mean arterial pressure greater than 65 mm Hg.

Following hemodynamic resuscitation and without sedative medications, the patient's neurologic examination demonstrated no response to noxious stimuli, sluggishly reactive pupils at 4 mm, forced downward gaze, limited vertical and horizontal eye movements on oculocephalic maneuvers, diminished corneal responses, and absent cough and gag reflexes. Emergent head CT revealed diffuse thick subarachnoid hemorrhage (SAH) with extension into all ventricles (FIGURE 2-7). The patient was diagnosed with World Federation of Neurological Surgeons Scale grade 5, modified Fisher Scale grade 4 acute SAH.

A large right frontal external ventricular drain (EVD) was urgently inserted, and CSF squirted out under high opening pressure. The patient was taken for digital subtraction angiography, which showed a large basilar tip aneurysm that was successfully coil embolized (FIGURE 2-8). The patient was subsequently admitted to the neurocritical care unit and received continuous vasopressor support for cardiogenic shock and mechanical ventilation for hypoxic respiratory failure. She remained obtunded and only grimaced sluggishly and sluggishly withdrew extremities to noxious stimuli.

Over the next 5 days, the patient's neurologic examination showed no improvement. Continuous EEG showed diffuse low-amplitude slowing with no epileptiform discharges. Her EVD was intermittently occluded from blood clots and had to be replaced twice. Her intracranial pressure remained below 20 mm Hg except for transient periods when the EVD was occluded. Troponin peaked at 15 ng/mL. She developed systemic inflammatory response syndrome, with persistent fever requiring

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**targeted temperature management with acetaminophen plus continuous surface cooling. Infectious workup found acute gram-positive pneumonia, and the patient was appropriately covered with broad-spectrum antibiotics. She had persistent acute kidney injury with oliguria and rising serum creatinine. Given the patient's progressive multiorgan failure, high-grade SAH, and known wishes, her family transitioned her to comfort-focused care and she was compassionately extubated.**

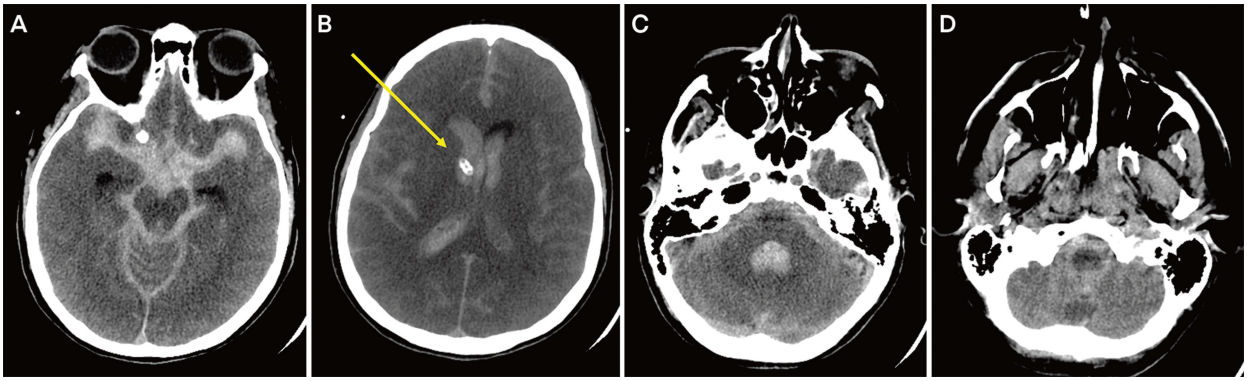


**FIGURE 2-7**
**Imaging of the patient in CASE 2-3. Axial noncontrast head CT shows extensive dense ("thick" in modified Fisher Scale) acute subarachnoid hemorrhage involving multiple cisterns (*A*) with extensive intraventricular extension from the lateral ventricles (*B*) through the fourth ventricle (*C, D*). *Yellow arrow* points to a large-bore external ventricular drain that terminates in the right lateral ventricle, inserted for emergent CSF diversion.**

**COMMENT**

This case illustrates a classic presentation of posterior circulation aneurysm rupture leading to high-grade SAH with associated acute cardiopulmonary failure, neurogenic stunned myocardium with takotsubo pattern on echocardiogram, and cardiogenic shock. This patient's hypoxic respiratory failure was likely caused by a combination of cardiogenic and neurogenic pulmonary edema. With extensive intraventricular blood extension, intermittent obstruction and clotting of even a large-bore EVD can occur, further complicating acute management of hydrocephalus. High-grade SAH increases a patient's risk for multiorgan dysfunction with SAH.

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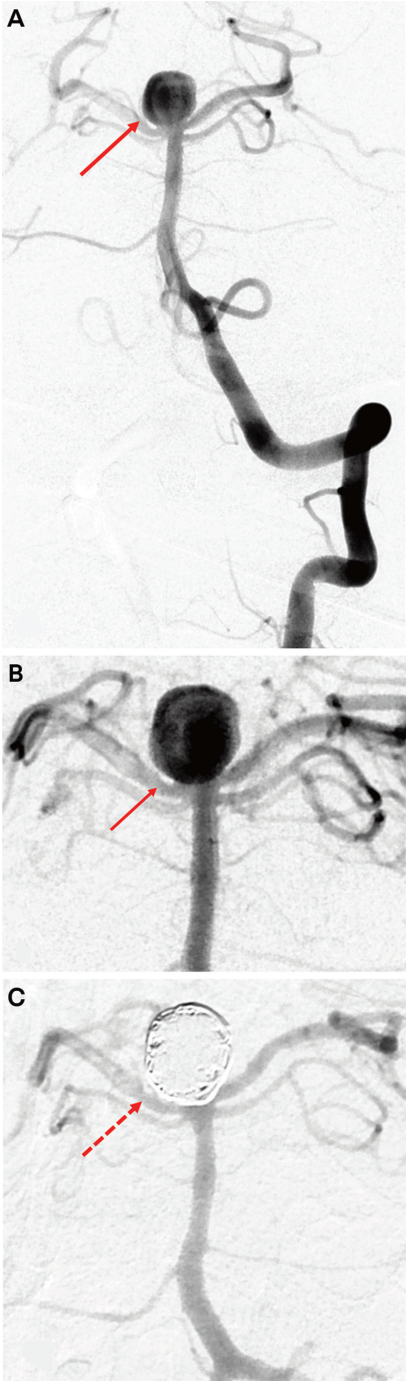


**FIGURE 2-8**
Cerebral angiography frontal view with left vertebral artery contrast injection of the patient in CASE 2-3 demonstrates the presence of a large basilar tip aneurysm (*A*), which was successfully coil-embolized (*B*, *C*). The *solid red arrow* points to the basilar tip aneurysm, and the *dashed red arrow* points to coiled aneurysm, which is no longer filling with contrast.

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from acute aspiration from nausea/vomiting, pulmonary ventilation/perfusion mismatch from calcium channel blocker use, cardiogenic pulmonary edema from neurogenic myocardial stunning, or, in rare cases, primary neurogenic pulmonary edema. To date, the precise mechanism of primary neurogenic pulmonary edema remains poorly understood, and treatment remains supportive care.[75] Timely diagnosis and treatment of acute respiratory insufficiency in SAH is important to minimize further brain injury due to hypoxia.

### Aneurysm Rebleeding and Timing of Aneurysm Surgery

Rerupture of the bleeding cerebral aneurysm following aneurysmal SAH is associated with very high mortality and morbidity. Short-term use of an antifibrinolytic drug (ε-aminocaproic acid) may be safe but does not reduce the rebleeding rate. Prolonged use (>72 hours) is associated with increased thrombotic complications.[76] Endovascular and open neurosurgical obliteration of the bleeding aneurysm effectively reduces the risk for aneurysm rebleeding. The best timing for aneurysm obliteration must balance the urgency to minimize rebleeding risk against the risks of aneurysm intervention, as aneurysm treatment itself is associated with cerebral ischemia and may potentiate SAH-associated brain injury when the injured brain is more vulnerable (refer to the section on early brain injury).[68,69] The cumulative rebleeding risk of a ruptured cerebral aneurysm is highest within the first 72 hours of aneurysm rupture (8% to 23%). Aneurysm obliteration has generally moved to within 72 hours of rupture since a clinical trial showed no outcome difference between aneurysm treatment within 3 days of rupture compared to delaying treatment after 7 days.[77] Guidelines from the AHA/ASA, the Neurocritical Care Society, and the European Stroke Organization all recommend aneurysm obliteration as early as feasible to minimize rebleeding risk. Currently, there are significant global practice variabilities on timing of aneurysm obliteration across centers.[78] The data on the benefit of aneurysm obliteration within 24 hours compared with 24 to 72 hours after bleeding are mixed, with one study showing possible worse outcome for aneurysms treated within 24 hours of rupture.[68,79,80]

### Aneurysm Treatment Approaches

Following acute stabilization of a patient with aneurysmal SAH, the next most important step is to secure the bleeding cerebral aneurysm. Surgical and endovascular options for aneurysm occlusion have improved significantly in recent decades and continue to evolve rapidly. The treatment approach often depends on aneurysm location, morphology, patient characteristics, and risk profiles. This is often a collaborative decision made by physicians with open and with endovascular expertise. General consensus is that, if amenable, endovascular approaches are preferred for posterior circulation aneurysm locations such as a basilar tip aneurysm. ISAT (the International Subarachnoid Aneurysm Trial) compared endovascular coiling to open surgical clipping in patients in whom the treating physicians felt that either approach would be appropriate. ISAT found that endovascular coiling is associated with higher odds of survival without disability at 1 year after SAH, and this risk reduction lasts for at least 7 years.[81] The endovascular approach is associated with a slightly higher rate of aneurysm recurrence; the long-term risk of recurrent SAH is low with either the endovascular or open surgical approach, although slightly higher with the endovascular approach.[82]

**KEY POINTS**

- The most common cause of spontaneous SAH is a ruptured cerebral aneurysm (85%). Approximately 10% to 15% of patients with SAH do not have an identifiable bleeding source; of these, approximately 38% have nonaneurysmal perimesencephalic SAH, which is a benign variant of SAH with generally excellent prognosis.
- Hyperacute life-threatening complications that can occur shortly after initial aneurysm bleeding include acute cardiopulmonary failure, acute hydrocephalus, diffuse cerebral edema, and aneurysm rebleeding.
- Acute symptomatic hydrocephalus can develop within minutes to days of aneurysm rupture and occurs in 20% of patients with SAH. Timely insertion of an external ventricular catheter for acute symptomatic hydrocephalus is lifesaving.
- Acute cardiopulmonary dysfunction is common in SAH and often requires critical care resuscitation and support. In severe cases, SAH may present with cardiac arrest. It is important to recognize aneurysmal SAH as a potential etiology in patients presenting with cardiac arrest, as delayed diagnosis is associated with high mortality.

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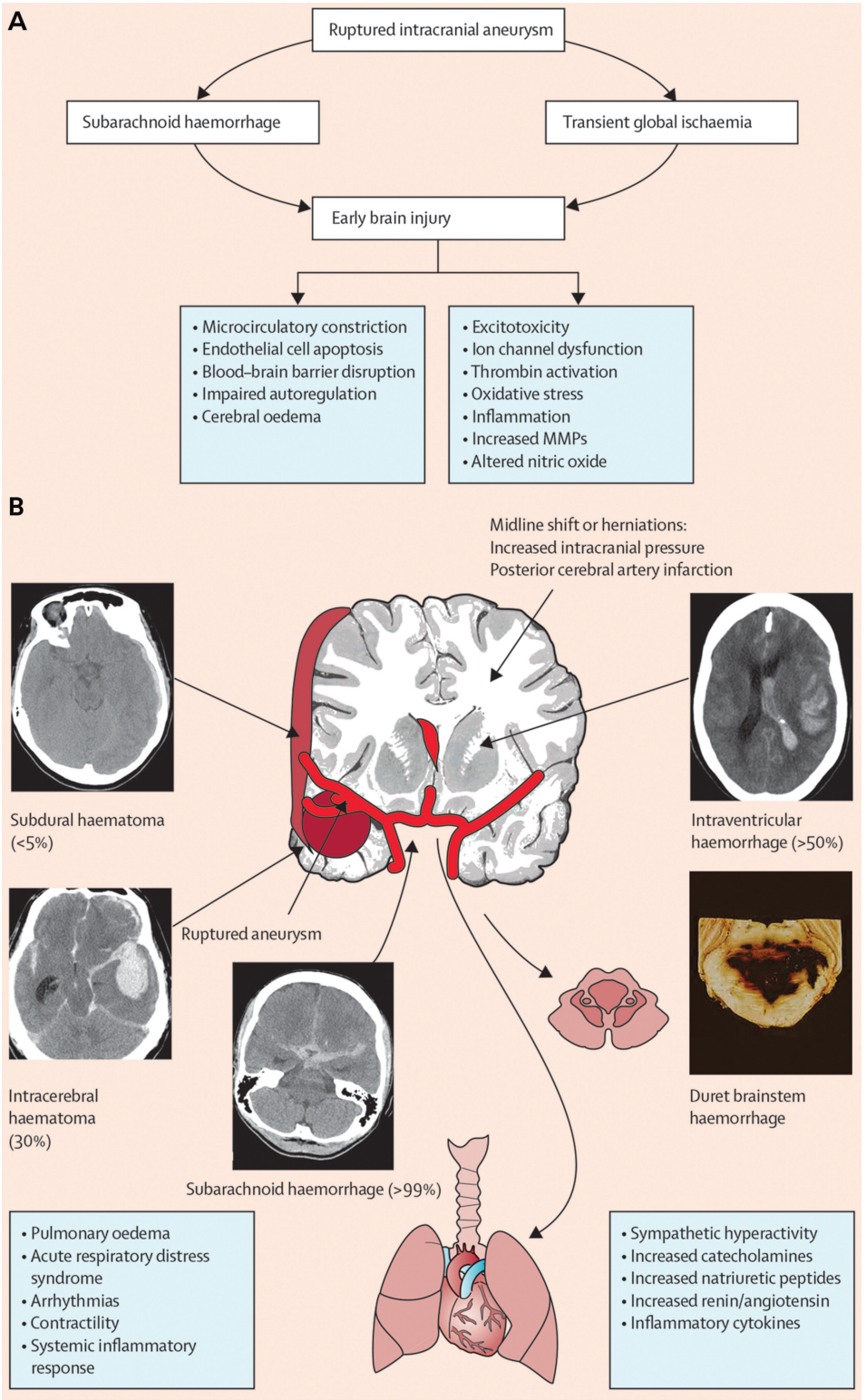


**FIGURE 2-9**

**Early brain injury mechanisms in aneurysmal subarachnoid hemorrhage. Hemorrhage into various compartments (subarachnoid, intraventricular, intracerebral, subdural) can cause brain shift, increased intracranial pressure, herniation, Duret brainstem hemorrhages, and death. Systemic effects of subarachnoid hemorrhage include cardiac and pulmonary complications. Brain injury from this condition initially is due to transient global ischemia and effects of the hemorrhage. Delayed neurologic complications can ensue.**

MMPs = matrix metalloproteinases.

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Since ISAT, endovascular techniques have evolved further, and newer devices such as flow-diverting stents and web devices have made it possible to treat aneurysms that had not been amenable to endovascular or surgical approaches. Treatment of ruptured and unruptured cerebral aneurysms has been shifting toward the endovascular approach, but open surgical approaches are still used, particularly in cases requiring hematoma evacuation for mass effect, prior incomplete aneurysm obliteration, or distal aneurysms. BRAT (the Barrow Ruptured Aneurysm Trial), performed 1 decade after ISAT, randomly assigned eligible patients to endovascular coil embolization or microsurgical clipping. The BRAT study found the endovascular arm had fewer poor outcomes at 1 year, but a substantial number of patients randomly assigned to the endovascular arm crossed over to the surgical clipping arm, suggesting surgical clipping remains an important alternative therapy.[83]

## SUBARACHNOID HEMORRHAGE–ASSOCIATED BRAIN INJURY

A prominent clinical feature of aneurysmal SAH is that a subset of patients will develop progressive neurologic deterioration and accrue brain injury despite the successful obliteration of the bleeding cerebral aneurysm and critical care support. Historically, this clinical neurologic deterioration has been thought to be caused by cerebral vasospasm and subsequent ischemic injury to the brain. Multiple terminologies have been used to refer to this phenomenon, including delayed cerebral ischemia (DCI). Much of the basic and clinical investigation on aneurysmal SAH in past decades was focused on prevention of cerebral vasospasm and DCI as a means to improve overall patient outcome and reduce morbidity and mortality. In the past decade, a series of large, well-powered, multicenter, randomized controlled trials testing various agents that had showed promising preclinical and early clinical signals in effectively reducing cerebral vasospasm failed to demonstrate outcome benefit despite angiographic improvement. A paradigm shift has since begun in the approach to understanding SAH-associated brain injuries and neurologic dysfunction, which is likely a complex multiphasic process involving multiple different pathophysiologic mechanisms.

### Phase 1: Early Brain Injury (0 to 72 Hours)

Early brain injury begins at the time of acute cerebral aneurysm rupture, which can lead to sudden transient ICP elevation, transient global ischemia, and a cascade of pathologic processes leading to injury and cell death (FIGURE 2-9).[84,85] Included in early brain injury is any direct brain tissue damage by an intracranial hematoma secondary to aneurysm rupture. Systemically, early brain injury is associated with multiple hyperacute extra–central nervous system acute organ dysfunctions (TABLE 2-7) and a systemic inflammatory response syndrome characterized by tachycardia, fever, tachypnea, and leukocytosis.[86]

### Phase 2: Delayed Cerebral Ischemia (3 to 21 days)

DCI (FIGURE 2-10[87]) is an SAH-associated brain injury process that typically develops 3 to 21 days following aneurysm rupture and remains one of the strongest predictors of poor outcome in patients with SAH who survived initial bleeding.[87,88] The term *ischemia* is misleading, as emerging evidence suggests that ischemia is only one of the many pathophysiologic processes involved in this phase of SAH-associated brain injury. Numerous overlapping terminologies with

**KEY POINTS**

- Neurogenic myocardial stunning with acute left ventricular dysfunction occurs in up to 30% of patients with SAH and can lead to reduced cardiac output and cardiogenic shock. A classic appearance of neurogenic stunned myocardium is left ventricle apical akinesis leading to ballooning of the apex during systole, often referred to as *takotsubo cardiomyopathy*. Timely appropriate critical care support is important to maintain adequate perfusion to the brain and body in patients with SAH with neurogenic stunned myocardium.

- Acute pulmonary dysfunction and hypoxic respiratory insufficiency are common after SAH and have multiple etiologies. Timely diagnosis and treatment of acute respiratory insufficiency in SAH is important to minimize further brain injury due to hypoxia.

- Aneurysm rerupture in SAH leads to high mortality and morbidity. Timely obliteration of a bleeding aneurysm by endovascular or microsurgical techniques very effectively reduces the risk of rerupture. Endovascular treatment of bleeding aneurysms is associated with higher survival and better outcomes and, when possible, is the preferred treatment modality. However, some aneurysms may not be amenable to endovascular approaches and may require microsurgical clipping.

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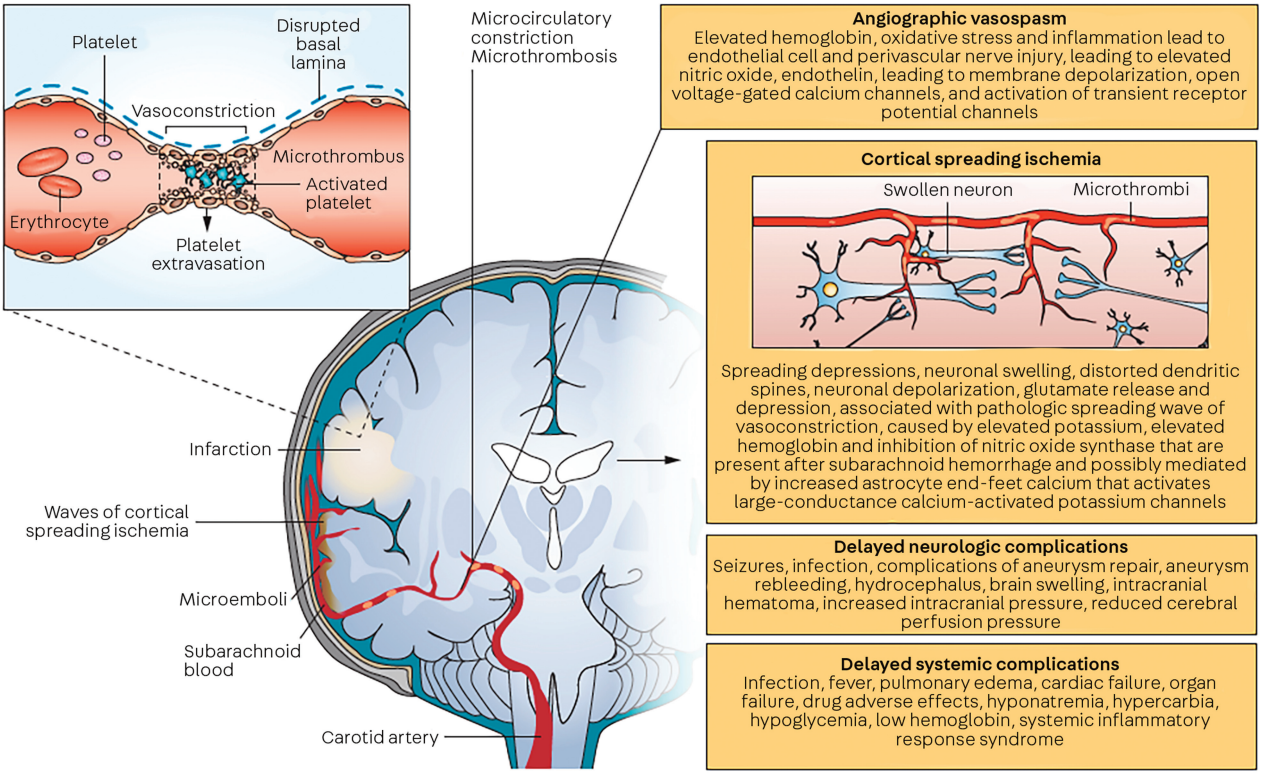
Platelet
Disrupted basal lamina
Vasoconstriction
Microthrombus
Activated platelet
Erythrocyte
Platelet extravasation
Microcirculatory constriction
Microthrombosis
Angiographic vasospasm
Elevated hemoglobin, oxidative stress and inflammation lead to endothelial cell and perivascular nerve injury, leading to elevated nitric oxide, endothelin, leading to membrane depolarization, open voltage-gated calcium channels, and activation of transient receptor potential channels
Cortical spreading ischemia
Swollen neuron
Microthrombi
Spreading depressions, neuronal swelling, distorted dendritic spines, neuronal depolarization, glutamate release and depression, associated with pathologic spreading wave of vasoconstriction, caused by elevated potassium, elevated hemoglobin and inhibition of nitric oxide synthase that are present after subarachnoid hemorrhage and possibly mediated by increased astrocyte end-feet calcium that activates large-conductance calcium-activated potassium channels
Infarction
Waves of cortical spreading ischemia
Microemboli
Subarachnoid blood
Carotid artery
Delayed neurologic complications
Seizures, infection, complications of aneurysm repair, aneurysm rebleeding, hydrocephalus, brain swelling, intracranial hematoma, increased intracranial pressure, reduced cerebral perfusion pressure
Delayed systemic complications
Infection, fever, pulmonary edema, cardiac failure, organ failure, drug adverse effects, hyponatremia, hypercarbia, hypoglycemia, low hemoglobin, systemic inflammatory response syndrome

**FIGURE 2-10**

**Delayed cerebral ischemia pathophysiology in aneurysmal subarachnoid hemorrhage.**

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variable definitions have been used in the literature to denote this second phase of brain injury and its clinical and possible associated radiologic features, leading to further confusion.[89] In 2019, a multidisciplinary international panel convened to establish common data elements for SAH to standardize naming and definition of SAH-associated terminologies and facilitate research advancement.[90,91] TABLE 2-8 summarizes common SAH-associated brain injuries and their definitions as used in recent large clinical trials.[92]

The clinical diagnosis of DCI is often challenging and involves a process of exclusion. A number of cohort studies have identified various different risk factors for DCI, but by far the most consistent and strongest predictor for DCI is the initial SAH clinical severity. The diagnosis of DCI in patients with high-grade SAH is even more difficult, as many patients may already demonstrate significant neurologic impairment or are sedated, limiting the sensitivity of clinical neurologic examination in screening for ongoing brain injury.[93] Significant practice variabilities exist in the diagnosis and monitoring for DCI, from clinical examination to a combination of clinical and diagnostic monitoring.

**CEREBRAL VASOSPASM.** A key feature in aneurysmal SAH is that up to 70% of all patients may subsequently develop cerebral vasoconstriction visible on DSA, typically between 3 and 21 days following initial aneurysm rupture. As summarized in FIGURE 2-10, current data suggest that large vessel cerebral



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vasospasm is one of the many processes that contribute to DCI in aneurysmal SAH. However, as ischemia from large vessel vasospasm is currently the only potentially clinically reversible etiology of DCI, the intensive care unit monitoring protocol for DCI is largely focused on early detection of cerebral vasospasm.

Similar to DCI, the concept of cerebral vasospasm is also plagued with multiple and overlapping terminologies and definitions (TABLE 2-8). Angiographic vasospasm usually refers to large vessel cerebral vasospasm visible on DSA with various degrees of severity. In SAH clinical trials, angiographic vasospasm is most commonly defined as reduction of cerebral artery diameter by more than two-thirds of its baseline caliber.[92] It is important to note that angiographic vasospasm may or may not be clinically symptomatic, and the severity of angiographic narrowing is not well correlated with clinical symptoms or SAH outcome. Although some degree of vasoconstriction/vasospasm is visible angiographically in up to 70% of patients with SAH, only 30% of all patients with SAH develop clinical symptoms attributable to ischemia from vasospasm visible on angiography. A common terminology used for this is *symptomatic vasospasm*, which is often used interchangeably with DCI or clinical deterioration due to DCI, among many others. Unlike angiographic vasospasm, the presence of symptomatic vasospasm is associated with DCI and poor outcome following SAH.[94,95] It important to note that in the SAH literature, symptomatic vasospasm and DCI often have overlapping definitions and may be referring to the same clinical phenomenon.

**Terminologies and Definitions in Subarachnoid Hemorrhage–Associated Brain Injury** TABLE 2-8

| Terminology | Definition |
|---|---|
| **Clinical deterioration caused by delayed cerebral ischemia** | The occurrence of focal neurologic impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect) or a decrease of at least 2 points on the Glasgow Coma Scale score (either on the total score or on one of its individual components) lasting at least 1 hour, not immediately apparent after aneurysm occlusion, and cannot be attributed to other causes by clinical, radiographic, or laboratory investigations |
| **Cerebral infarction due to delayed cerebral ischemia** | The presence of cerebral infarction on CT or MRI of the brain within 6 weeks of subarachnoid hemorrhage (SAH) or proven at autopsy, not present on CT or MRI between 24 and 48 hours after aneurysm occlusion |
| **Delayed ischemic neurologic deficit[92]** | A decrease of ≥2 points on the modified Glasgow Coma Scale score or an increase of ≥2 points on the abbreviated National Institutes of Health Stroke Scale score lasting for at least 2 hours |
| **Angiographic cerebral vasospasm** | Constriction of cerebral arteries visible on diagnostic cerebral angiography following SAH; in most recent large clinical trials, vasospasm is defined as reduction of cerebral arterial diameter by more than two-thirds from baseline[92]; not clearly associated with delayed cerebral ischemia or SAH functional outcome |
| **Symptomatic cerebral vasospasm** | Patients with SAH develop clinical symptoms attributable to ischemia from visible vasospasm on angiography |

CT = computed tomography; MRI = magnetic resonance imaging.



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## CASE 2-1B

Following successful endovascular aneurysm coil embolization, the patient in CASE 2-1A was admitted to the neurocritical care unit. She arrived intubated with oxygen saturation of 96% on 80% $FIO_2$ and positive end-expiratory pressure (PEEP) of 5 cm $H_2O$. Chest x-ray showed evidence of gross aspiration. Bedside bronchoscopy successfully removed gastric content, and her oxygenation improved. Off sedation, the patient was able to open her eyes to voice and sluggishly follow commands. Her brainstem reflexes were intact. She moved all extremities equally with antigravity strength. She was started on nimodipine 60 mg through a nasogastric tube every 4 hours for 21 days. Because of clinical seizurelike activity at initial presentation, she was continued on levetiracetam 1000 mg through a nasogastric tube 2 times a day for seizure prophylaxis. She was also started on low-molecular-weight heparin injections for venous thromboembolism prophylaxis.

On post–subarachnoid hemorrhage (SAH) day 2, the patient was extubated successfully. She was oriented to self and place but not to time and was intermittently drowsy. She began daily transcranial Doppler ultrasound studies for monitoring of delayed cerebral vasospasm. IV boluses were used to maintain euvolemia, measured by total fluid balance and clinical assessment. Her mean arterial pressure was 70 mm Hg to 80 mm Hg.

On post-SAH day 5, the patient became febrile to 38.5 °C (101.3 °F) with leukocytosis. Chest x-ray, urinalysis, CSF analysis, and blood culture were all negative. Venous duplex studies did not find any deep venous thrombosis as the potential occult cause of fever, and she was started on acetaminophen for fever control. She had no focal weakness but appeared impulsive and delirious. She developed tachycardia, with heart rate of approximately 100 beats/min to 110 beats/min, and hypertension with systolic blood pressure 170 mm Hg to 180 mm Hg. The Lindegaard ratios on transcranial Doppler were 2.9 on the left and 3.2 on the right (normal reference <3), suggesting possible mild vasospasm in the right middle cerebral artery.

The next morning, on post-SAH day 6, the patient remained febrile and developed voluminous urine output at 400 mL/h to 600 mL/h, and plasma sodium dropped to 132 mmol/L, consistent with cerebral salt wasting syndrome. She then suddenly developed bilateral lower extremity plegia with increased tone. Her intracranial pressure was 15 mm Hg. She was immediately resuscitated with 30 mL/kg of 4 °C (39.2 °F) IV normal saline (0.9% sodium chloride) bolus. Emergent head CT showed no new hemorrhage or infarct. She was started on a norepinephrine infusion through a subclavian central line to maintain systolic blood pressure at 180 mm Hg to 220 mm Hg and taken emergently for digital subtraction angiography (DSA), which showed severe flow-limiting vasospasm in multiple segments of bilateral anterior cerebral arteries (FIGURES 2-1I) and mild to moderate vasospasm of right middle cerebral artery M2 segments (FIGURES 2-1IA and 2-1IB). She was treated with 10 mg intraarterial nicardipine injections to both internal carotid arteries. Subsequently, the patient's new neurologic deficits resolved. She remained on a norepinephrine drip to maintain systolic blood pressure at 180 Hg mm to 220 mm Hg. For

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high-volume urine output and hyponatremia consistent with cerebral salt wasting syndrome, she was treated with hourly IV fluid boluses to replace urinary fluid loss and to maintain even to 500 mL positive total body fluid balance. She was started on fludrocortisone, and her polyuria improved.

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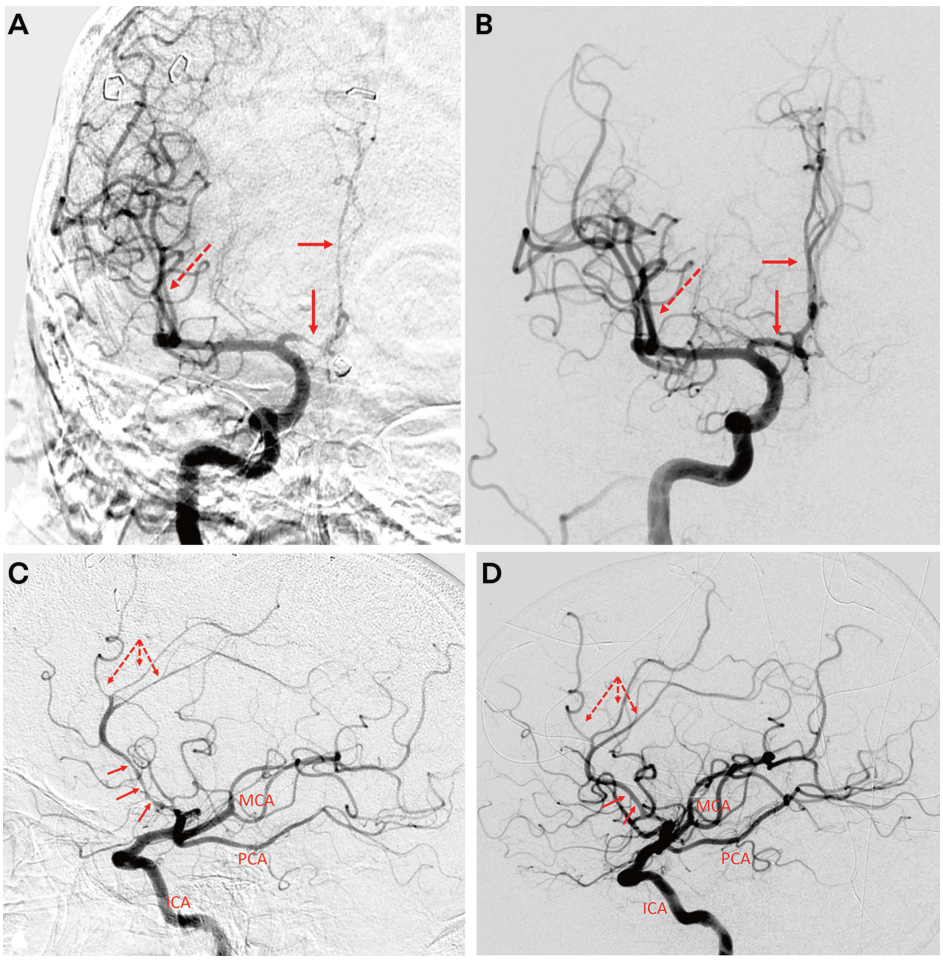


**FIGURE 2-11**

**Imaging of the patient in CASE 2-1B. Panels *A* and *C* are cerebral angiography images from post–subarachnoid hemorrhage (SAH) day 6. Panels *B* and *D* are cerebral angiography images from day of initial presentation with SAH. Anterior-posterior view of right internal carotid artery (ICA) injection from emergent digital subtraction angiography (DSA) following acute deterioration on post–SAH day 6 (*A*) demonstrates severe vasospasm (*solid red arrows*) in distal A1 and throughout subsequent segments of the right anterior cerebral artery (ACA) with significantly delayed arterial filling in the ACA territory compared to DSA obtained on day of admission (*B*). Calibers of M2 branches of the right middle cerebral artery (MCA) are also reduced (*dashed red arrow*) compared to DSA from day of admission, consistent with mild to moderate vasospasm. Oblique view of left ICA injection from emergent DSA following acute deterioration on post–subarachnoid hemorrhage day 6 (C) demonstrates severe vasospasm (*solid red arrows*) with sausage appearance in A2 branch and diffuse vasospasm of its distal segments (*dashed red arrows*) of the left ACA with delayed arterial filling in the ACA territory compared to DSA obtained on day of admission (*D*).**

PCA = posterior cerebral artery.

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CONTINUED FROM PAGE 1227

**On post-SAH day 8, the patient again acute bilateral lower extremity developed weakness, DSA showed persistent severe bilateral anterior cerebral artery vasospasm treated with angioplasty of the proximal anterior cerebral arteries and intraarterial nicardipine infusion through both internal carotid arteries. Postendovascular rescue, the patient's new neurologic deficits resolved.**

**Over the next few days, the patient continued on supportive therapy for symptomatic cerebral vasospasm, including fluid resuscitation to maintain euvolemia, induced hyperdynamic therapy to maintain systolic blood pressure at 180 mm Hg to 240 mm Hg, continued CSF diversion, and targeted temperature management to maintain euthermia (temperature target 36.5 °C to 37.5 °C [97.7 °F to 99.5 °F]). The patient did not develop any further acute neurologic symptoms, and her clinical condition gradually improved, with less fever and resolving polyuria, and she became more alert and oriented. The patient was gradually weaned off the norepinephrine drip provided she had no new neurologic deterioration. Her external ventricular drain was removed, and she was able to transfer out of the intensive care unit on post-SAH day 17. She had significant deconditioning and protein malnutrition following the prolonged critical illness and required physical therapy for strength and coordination training. On post-SAH day 20, she was discharged to home.**

## COMMENT

This case illustrates the classic presentation, disease course, clinical monitoring, and treatment considerations for severe symptomatic cerebral vasospasm following aneurysmal SAH. This case also illustrates how transcranial Doppler as a screening modality may not detect all clinically significant vasospasm, particularly in more distal segments of cerebral arteries such as the severe A2 segment vasospasm in this case. This patient had refractory cerebral vasospasm requiring repeated endovascular rescue therapy and induced hyperdynamic therapy with inotropic vasopressors such as norepinephrine to maintain cerebral perfusion. In this case, timely diagnosis of symptomatic vasospasm with rapid resuscitation to correct hypovolemia from cerebral salt wasting and endovascular rescue therapy likely prevented sustained delayed cerebral ischemia, and the patient had a relatively good outcome at hospital discharge. Many patients with favorable outcome at hospital discharge (modified Rankin Scale score of <3) still experience significant disabling symptoms, which can include headaches, cognitive and memory dysfunction, mood disorder, sexual dysfunction, mental and physical fatigue, sleep disorders, and anosmia, even at 1 year following SAH.[97] Long-term follow-up, consultation with the physical medicine and rehabilitation team, and targeted therapy are important for continued care of survivors of aneurysmal SAH.

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Transcranial Doppler (TCD) ultrasound monitoring of cerebral artery flow velocity is commonly used as a low-risk noninvasive tool to monitor for the presence of cerebral vasospasm following acute SAH. TCD has reasonable sensitivity and specificity to detect vasospasm in the circle of Willis cerebral arteries, particularly the proximal segments of the middle cerebral artery (MCA) and internal carotid artery (ICA). TCD is less reliable in detecting vasospasm in the anterior cerebral artery (ACA) branches and posterior circulation arteries.[96] The Lindegaard ratio, defined as the ratio of mean MCA flow velocity divided by mean ICA flow velocity, is typically used to diagnose vasospasm in the MCA when the ratio is above 3. However, it is important to note that the sensitivity and specificity of TCD for detecting cerebral vasospasm is operator dependent, that different laboratories may use different threshold values for cerebral vasospasm, and that some patients do not have adequate temporal bone windows to allow detection of TCD signals. When using TCD to monitor cerebral vasospasm, results must be interpreted with clinical correlation, and negative TCD studies do not rule out the presence of vasospasm or the risk for symptomatic DCI (**CASE 2-1B**). More advanced modes of TCD have been used to detect cerebral autoregulation dysfunction and microemboli in SAH and DCI, but the use of these techniques remains experimental at this time.[98,99] DSA remains the gold standard for diagnosis of large- and medium-caliber cerebral artery vasospasm.

In patients at high risk for severe angiographic vasospasm or those who have known angiographic vasospasm, the acute onset of neurologic symptoms attributable to ischemia corresponding to the vascular territory at risk likely represents acute cerebral hypoperfusion that may lead to permanent cell death if perfusion is not rapidly restored. This forms the basis of many empiric treatment protocols for symptomatic vasospasm/DCI, such as hemodynamic augmentation to enhance cerebral blood flow and endovascular rescue therapy in acute symptomatic vasospasm. No high-quality clinical trial data are available to guide management in these clinical scenarios. As a result, significant variabilities in management approaches exist, and this remains one of the most debated areas of SAH management.

Common forms of acute endovascular rescue therapy involve intraarterial infusion of a vasodilatory drug, such as nicardipine or verapamil, and balloon angioplasty.[9,87] These interventions have not been studied in large randomized clinical trials, and their global efficacy remain unknown. Use of endovascular therapy is very much dependent on local practice patterns at each center. These interventions can be associated with significant procedure-related complications. Current expert recommendations suggest reserving these for patients with clinically symptomatic vasospasm rather than empirically treating all patients with angiographic or TCD evidence of vasospasm.[5,9] It is important to note that in patients with severe clinical grade SAH who have severe disorders of consciousness or already have a severe neurologic deficit from early brain injury, their poor baseline examination makes the diagnosis of symptomatic vasospasm difficult and highly variable between clinicians. Some centers use advanced multimodal monitoring techniques or imaging modalities, such as CT or magnetic resonance perfusion studies, to assist in treatment decision making. Currently, no systematic study data on these approaches are available, and their use remains experimental.

**KEY POINTS**

- A prominent clinical feature of SAH is that a subset of patients will develop progressive neurologic deterioration and additional brain injury despite the successful obliteration of the bleeding cerebral aneurysm and critical care support. Brain injury following SAH is multiphasic and caused by multiple pathophysiologic processes, including ischemia from vasospasm.
- Early brain injury following SAH begins at the time of acute cerebral aneurysm rupture when sudden intracranial pressure elevation causes transient global cerebral ischemia and brain tissue damage by intracranial hematoma.
- Delayed cerebral ischemia is an SAH-associated brain injury process that typically develops 3 to 21 days following aneurysm rupture and remains the strongest predictor of poor outcome. The term *ischemia* is misleading, as many different pathophysiologic mechanisms contribute to this phase of brain injury.

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**PREVENTION AND TREATMENT OF DELAYED CEREBRAL ISCHEMIA BEYOND TREATMENT OF ANGIOGRAPHIC VASOSPASM.** To date, the only therapeutic agent with Class I evidence for decreasing risk of poor outcome in SAH is nimodipine started within 96 hours of initial hemorrhage and continued at 60 mg every 4 hours for 21 consecutive days.[100] A common misconception is that nimodipine exerts therapeutic benefit through reducing cerebral vasospasm. In a randomized clinical trial, the rate of angiographic vasospasm was similar between treatment arms, whereas the nimodipine arm had a reduced rate of DCI.

Numerous other therapeutics, such as fasudil, cilostazol, intrathecal fibrinolytics, and intrathecal vasodilators such as nicardipine, have been evaluated in smaller clinical trials and meta-analyses and are thought to demonstrate possible efficacy in protection against DCI and improve aneurysmal SAH outcome. Although more data are needed and only low-grade evidence supports the use of these agents, some centers empirically use these agents for

**TABLE 2-9** Randomized Controlled Clinical Trials of Delayed Cerebral Ischemia Therapeutics

| Agent | Mechanism of action | Dose studied | Result |
|---|---|---|---|
| **Nimodipine (1983)[102]** | Calcium channel blocker | 60 mg orally every 4 hours for 21 days | Reduced severe disability/death post-subarachnoid hemorrhage (SAH); no change in incidence of vasospasm |
| **Nicardipine (1992)[103,104]** | Calcium channel blocker | 0.075 mg/kg/h IV for 14 days | Reduced incidence of symptomatic and angiographic vasospasm; no difference in SAH outcome |
| **Tirilazad mesylate (1992-1999)[105-107]** | Free radical scavenger | Multiple doses were studied | Reduced incidence of symptomatic vasospasm and infarct; no change in outcome |
| **Clazosentan (2011) CONSCIOUS-2 (Clazosentan in Reducing Vasospasm-related Morbidity and All-cause Mortality in Adult Patients With Aneurysmal Subarachnoid Hemorrhage Treated by Surgical Clipping)[92]** | Selective endothelin-1b receptor antagonist | 5 mg/h for 14 days | Reduced need for endovascular rescue therapy for vasospasm; no difference in SAH outcome |
| **Magnesium (2012) MASH-2 (Magnesium for Aneurysmal Subarachnoid Hemorrhage)[108]** | Multiple mechanisms | 64 mmol/d IV infusion | No difference in SAH outcome |
| **Simvastatin (2014) STASH (Simvastatin in Aneurysmal Subarachnoid Hemorrhage)[109]** | Multiple mechanisms | 40 mg/d orally for 21 days | No difference in SAH outcome at 6 months |
| **Intrathecal nimodipine (2020) NEWTON2 (Study of EG-1962 Compared to Standard of Care Oral Nimodipine in Adults With Aneurysmal Subarachnoid Hemorrhage)[101]** | Calcium channel blocker | Extended release 600 mg nimodipine bound to microparticle | Trial stopped early because of futility; no difference in rate of angiographic vasospasm or poor SAH outcome |



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DCI treatment or prevention. Meanwhile, several therapeutics have been tested in large well-powered multicenter randomized clinical trials and showed no efficacy in improving SAH functional outcome, although some reduced the incidence of angiographic vasospasm.[92] The 2020 NEWTON2 (Study of EG-1962 Compared to Standard of Care Oral Nimodipine in Adults With Aneurysmal Subarachnoid Hemorrhage) randomized clinical trial on intrathecal nimodipine to improve SAH outcome was stopped early following interim analysis demonstrating futility.[101] TABLE 2-9[102-109] summarizes the large randomized clinical trial evidence in DCI prevention to date.

Intravascular hypovolemia is associated with DCI and unfavorable neurologic outcomes in aneurysmal SAH.[87] Hypovolemia is a particular concern in aneurysmal SAH as a subset of patients develop SAH-associated cerebral salt wasting syndrome, in which rapid natriuresis may lead to acute intravascular hypovolemia and hyponatremia. Historically, inducing intravascular hypervolemia as part of the hypervolemic, hypertensive, and hemodilutional (Triple H) therapy was used to support patients with DCI or cerebral vasospasm or even used prophylactically before clinical evidence of DCI or vasospasm was seen. Studies have since shown that prophylactic use of Triple H therapy is not associated with any improved SAH outcome but increases cardiopulmonary complications and is not recommended in modern neurocritical care practice.[87] Current guidelines by the Neurocritical Care Society and the AHA/ASA recommend avoiding hypovolemia and maintaining intravascular euvolemia in aneurysmal SAH (TABLE 2-10[110]).

## ACUTE COMPLICATIONS OF SUBARACHNOID HEMORRHAGE AND CRITICAL CARE MANAGEMENT CONSIDERATIONS

Acute SAH is a critical illness that often leads to multiorgan dysfunction in addition to brain injury. Optimal neurocritical care requires support and optimization of both acute brain dysfunction and systemic dysfunctions that may secondarily worsen brain injury processes. After patients with SAH survive the hyperacute period and aneurysm intervention and while their brains are susceptible to DCI, patients with SAH often develop some, if not all, of the following complications commonly seen during acute SAH course. These common complications and their management recommendations per the latest AHA/ASA and Neurocritical Care Society guidelines are summarized in TABLE 2-10.

### Seizures and Nonconvulsive Status Epilepticus

The clinical presentation of acute onset of aneurysm rupture or rerupture can include seizurelike symptoms (CASE 2-1A). Given the emergent and critical onset of these symptoms, confirmatory testing with EEG is often impractical when these symptoms are present. Up to 26% of patients with aneurysmal SAH may present with seizurelike symptoms at onset.[5,9] Although no high-level evidence exists to support clinical efficacy, many clinicians empirically load anticonvulsants during hyperacute resuscitation until the patient is stabilized. Clinicians may choose to continue anticonvulsant use until the bleeding cerebral aneurysm is surgically obliterated based on the assumption that seizures may cause rapid spikes in blood pressure and increase the risk for aneurysm rebleed. Following successful obliteration of the bleeding aneurysm, discontinuation of anticonvulsants can be considered. It is important to note that nonconvulsive seizures and nonconvulsive status epilepticus are seen in up to 18% of comatose

**KEY POINTS**

- Multiple overlapping terminologies used to describe secondary neurologic deterioration and brain injury lead to confusion over clinical entities and monitoring approaches. Consensus common data elements and definitions for clinical deterioration due to delayed cerebral ischemia, cerebral infarction due to delayed cerebral ischemia, angiographic cerebral vasospasm, and symptomatic cerebral vasospasm are available and should be used to minimize confusion.

- Up to 70% of all patients with aneurysmal SAH may subsequently develop visible cerebral vasoconstriction on digital subtraction angiography between 3 and 21 days following initial aneurysm rupture, but only 30% will develop clinical symptoms attributable to ischemia from vasospasm. Symptomatic vasospasm is associated with delayed cerebral ischemia and unfavorable SAH outcome, whereas angiographic vasospasm is not.

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TABLE 2-10 **Summary of Key Management Recommendations from the American Heart Association/American Stroke Association and Neurocritical Care Society Guidelines**[a]

| Treatment decision | American Heart Association/ American Stroke Association[5,b] | Neurocritical Care Society[9,c] |
|---|---|---|
| **Hospital/system characteristics** | Low-volume hospitals (eg, fewer than 10 subarachnoid hemorrhage [SAH] cases per year) should consider early transfer of patients with SAH to high-volume centers (eg, more than 35 SAH cases per year) with experienced cerebrovascular surgeons, endovascular specialists, and multidisciplinary neurointensive care services (Class I, Level B).<br><br>After discharge, it is reasonable to refer patients with SAH for a comprehensive evaluation, including cognitive, behavioral, and psychosocial assessments (Class IIa, Level B). | Patients with SAH should be treated at high-volume centers (moderate quality of evidence, strong recommendation).<br><br>High-volume centers should have appropriate specialty neurointensive care units, neurointensivists, vascular neurosurgeons, and interventional neuroradiologists to provide the essential elements of care (moderate quality of evidence, strong recommendation). |
| **Aneurysm treatment** | Surgical clipping or endovascular coiling of the ruptured aneurysm should be performed as early as feasible in the majority of patients to reduce the rate of rebleeding after SAH (Class I, Level B).<br><br>For patients with ruptured aneurysms judged to be technically amenable to either endovascular coiling and neurosurgical clipping, endovascular coiling should be considered (Class I, Level B).<br><br>Complete obliteration of the aneurysm is recommended whenever possible (Class I, Level B). Stenting of a ruptured aneurysm is associated with increased morbidity and mortality (Class III, Level C).<br><br>For patients with an unavoidable delay in obliteration of aneurysm, a significant risk of rebleeding, and no compelling medical contraindications, short-term (less than 72 hours) therapy with tranexamic acid or aminocaproic acid is reasonable to reduce the risk of early aneurysm rebleeding (Class IIa, Level B). | Early aneurysm repair should be undertaken, when possible and reasonable, to prevent rebleeding (high quality of evidence, strong recommendation).<br><br>An early, short course of antifibrinolytic therapy prior to early aneurysm repair (begun at diagnosis and continued up to the point at which the aneurysm is secured or at 72 hours postictus, whichever is shorter) should be considered (low quality of evidence, weak recommendation).<br><br>Delayed (more than 48 hours after the ictus) or prolonged (more than 3 days) antifibrinolytic therapy exposes patients to side effects of therapy when the risk of rebleeding is sharply reduced and should be avoided (high quality of evidence, strong recommendation). |
| **Blood pressure control** | Between the time of SAH symptom onset and aneurysm obliteration, blood pressure should be controlled with a titratable agent to balance the risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion pressure (Class I, Level B).<br><br>The magnitude of blood pressure control to reduce the risk of rebleeding has not been established, but a decrease in systolic blood pressure to less than 160 mm Hg is reasonable (Class IIa, Level C). | Treat extreme hypertension in patients with an unsecured, recently ruptured aneurysm. Modest elevations in blood pressure (mean blood pressure of less than 110 mm Hg) do not require therapy. Premorbid baseline blood pressures should be used to refine targets and hypotension should be avoided (low quality of evidence, strong recommendation). |

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| Treatment decision | American Heart Association/ American Stroke Association[5,b] | Neurocritical Care Society'[9,c] |
|---|---|---|
| **Intravascular volume status** | Maintenance of euvolemia and normal circulating blood volume is recommended to prevent delayed cerebral ischemia (Class I, Level B). | Intravascular volume management should target euvolemia and avoid prophylactic hypervolemic therapy. In contrast, there is evidence for harm from aggressive administration of fluid aimed at achieving hypervolemia (moderate quality of evidence, strong recommendation). |
| **Cardiopulmonary complications** | No recommendations given. | Baseline cardiac assessment with serial enzymes, ECG, and echocardiography is recommended, especially in patients with evidence of myocardial dysfunction (low quality of evidence, strong recommendation).<br>Monitoring of cardiac output may be useful in patients with evidence of hemodynamic instability or myocardial dysfunction (low quality of evidence, strong recommendation). |
| **Seizures** | The use of prophylactic anticonvulsants may be considered in the immediate posthemorrhagic period (Class IIb, Level B).<br>The routine long-term use of anticonvulsants is not recommended (Class III, Level B). | Routine use of anticonvulsant prophylaxis with phenytoin is not recommended after SAH (low quality of evidence, strong recommendation).<br>If anticonvulsant prophylaxis is used, a short course (3–7 days) is recommended (low quality of evidence, weak recommendation).<br>Continuous EEG monitoring should be considered in patients with poor-grade SAH who fail to improve or who have neurologic deterioration of undetermined etiology (low quality of evidence, strong recommendation). |
| **Fever treatment** | Aggressive control of fever to a target of normothermia by use of standard or advanced temperature modulating systems is reasonable in the acute phase of SAH (Class IIa, Level B). | During the period of risk for delayed cerebral ischemia, control of fever is desirable; intensity should reflect the individual patient's relative risk of ischemia (low quality of evidence, strong recommendation).<br>Surface cooling or intravascular devices are more effective and should be employed when antipyretics fail in cases where fever control is highly desirable (high quality of evidence, strong recommendation). |
| **Glucose control** | Careful glucose management with strict avoidance of hypoglycemia may be considered as part of the general critical care management of patients with SAH (Class IIb, Level B). | Hypoglycemia (serum glucose of less than 80 mg/dL) should be avoided (high quality of evidence, strong recommendation).<br>Serum glucose should be maintained below 200 mg/dL (moderate quality of evidence, strong recommendation). |
| **Deep vein thrombosis prophylaxis** | Heparin-induced thrombocytopenia and deep vein thrombosis are relatively frequent complications after SAH. Early identification and targeted treatment are recommended, but further research is needed to identify the ideal screening paradigms (Class I, Level B). | Measures to prevent deep vein thrombosis should be employed in all patients with SAH (high quality of evidence, strong recommendation).<br>The use of unfractionated heparin for prophylaxis could be started 24 hours after undergoing aneurysm obliteration (moderate quality of evidence, strong recommendation). |

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| Treatment decision | American Heart Association/ American Stroke Association[5,b] | Neurocritical Care Society'[9,c] |
|---|---|---|
| **Delayed cerebral ischemia** | Oral nimodipine should be administered to all patients with SAH (Class I, Level A).<br><br>Maintenance of euvolemia and normal circulating blood volume is recommended to prevent delayed cerebral ischemia (Class I, Level B).<br><br>Prophylactic hypervolemia or balloon angioplasty before the development of angiographic spasm is not recommended (Class III, Level B).<br><br>Transcranial Doppler is reasonable to monitor for the development of arterial vasospasm (Class IIa, Level B).<br><br>Perfusion imaging with CT or MRI can be useful to identify regions of potential brain ischemia (Class IIa, Level B).<br><br>Induction of hypertension is recommended for patients with delayed cerebral ischemia unless blood pressure is elevated at baseline or cardiac status precludes it (Class I, Level B).<br><br>Cerebral angioplasty and/or selective intraarterial vasodilator therapy is reasonable in patients with symptomatic vasospasm, particularly those who are not responding to hypertensive therapy (Class IIa, Level B). | Oral nimodipine (60 mg every 4 hours) should be administered after SAH for a period of 21 days (high quality of evidence, strong recommendation).<br><br>The goal should be maintaining euvolemia, rather than attempting hypervolemia (moderate quality of evidence, strong recommendation).<br><br>Transcranial Doppler may be used for monitoring and detection of large artery vasospasm with variable sensitivity (moderate quality of evidence, strong recommendation).<br><br>Digital subtraction angiography is the gold standard for detection of large artery vasospasm (high quality of evidence, strong recommendation).<br><br>Patients clinically suspected of delayed cerebral ischemia should undergo a trial of induced hypertension (moderate quality of evidence, strong recommendation).<br><br>Endovascular treatment using intraarterial vasodilators and/or angioplasty may be considered for vasospasm-related delayed cerebral ischemia (moderate quality of evidence, strong recommendation). |
| **Anemia and transfusion** | The use of packed red blood cell transfusion to treat anemia might be reasonable in patients with SAH who are at risk of cerebral ischemia. The optimal hemoglobin goal is still to be determined (Class IIb, Level B). | Patients should receive packed red blood cell transfusions to maintain hemoglobin concentration above 8–10 g/dL (moderate quality of evidence, strong recommendation). |
| **Hyponatremia** | The use of fludrocortisone acetate and hypertonic saline solution is reasonable for preventing and correcting hyponatremia (Class IIa, Level B). | Fluid restriction should not be used to treat hyponatremia (weak quality of evidence, strong recommendation).<br><br>Early treatment with hydrocortisone or fludrocortisone may be used to limit natriuresis and hyponatremia (moderate quality of evidence, weak recommendation).<br><br>Mild hypertonic saline solutions can be used to correct hyponatremia (very low quality of evidence, strong recommendation). |

CT = computed tomography; ECG = electrocardiogram; EEG = electroencephalogram; MRI = magnetic resonance imaging.

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[b] American Heart Association/American Stroke Association recommendations follow the American Heart Association Stroke Council's methods of classifying the level of certainty of the treatment effect and the class of evidence.

[c] For the Neurocritical Care Society's guidelines, the quality of the data was assessed and recommendations developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system.



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SAH patients and they are associated with unfavorable outcome.[111,112] As a result, experts recommend continuous EEG studies in patients with high-grade SAH who remain comatose or encephalopathic following resuscitation. Currently, no data are available on whether continuous EEG or anticonvulsant use affects SAH outcome. For more information on the use of continuous EEG in the management of SAH, refer to the article "Seizures, Status Epilepticus, and Continuous EEG in the Intensive Care Unit" by Eric S. Rosenthal, MD,[113] in this issue of *Continuum*.

Following obliteration of bleeding cerebral aneurysms, cohort studies suggest that in patients who did not present with seizurelike events, discontinuation of anticonvulsants is safe, not associated with increased seizures, and, in fact, may be associated with more favorable SAH outcome and improved neurocognitive recovery, particularly with the use of phenytoin.[114-116] Currently, very limited data are available on whether acute anticonvulsant use impacts the risk for developing long-term epilepsy, which occurs in 2% of survivors of SAH.[1]

### Fever and Systemic Inflammatory Response Syndrome

Fever is a common symptom in patients with hemorrhagic brain injuries. Following SAH, up to 70% of patients develop fever during the acute clinical course, which may be infectious, noninfectious/inflammatory, or central/neurogenic in etiology.[5,9] Febrile symptoms often parallel the onset of DCI and overall critical illness severity; in patients with severe-grade SAH with multiorgan dysfunction, it may be difficult to rule out infectious etiologies. Fever is associated with higher SAH clinical severity and worse outcome, and small studies of targeted temperature management strategies suggest there may be a signal toward improved SAH outcome.[117] Current guidelines recommend fever control, although larger clinical trials are still needed to determine whether and how much fever control may be beneficial in SAH.

Systemic inflammatory response syndrome, characterized by a combination of two or more clinical features of tachycardia, tachypnea, fever or hypothermia, and leukocytosis or leukopenia, is a clinical syndrome initially defined to capture inflammatory response to acute systemic disease such as sepsis. Systemic inflammatory response syndrome is prevalent in the clinical course of acute SAH and is associated with higher initial SAH severity, larger hematoma, and unfavorable outcomes. Whether systemic inflammation exerts independent effects on worsening SAH-associated brain injury is currently unknown and is an area of active investigation.[86]

### Chronic Shunt-dependent Hydrocephalus

A subset of patients with SAH who required EVDs for CSF diversion may fail to wean from CSF drainage and require long-term CSF diversion via various types of shunting devices. The timing and method of EVD weaning following SAH and the threshold to convert to long-term CSF shunting are highly variable between centers. General risk factors for developing shunt-dependent hydrocephalus following SAH include older age, high clinical SAH grade, the need for EVD placement, a larger amount of SAH blood, and intraventricular hemorrhage.[118] Although various small studies have investigated whether medications (such as dexamethasone) or other management strategies can prevent progression to chronic shunt-dependent hydrocephalus following SAH,[119] insufficient clinical evidence is available to support any prophylactic strategy.

**KEY POINTS**

- Transcranial Doppler (TCD) ultrasound is a common modality used to monitor for the development of vasospasm. TCD has adequate sensitivity to detect vasospasm in the circle of Willis vessels but is less reliable for distal vessel segments and posterior circulation vessels. The sensitivity and specificity of TCD are operator and laboratory dependent. TCD results must be interpreted with clinical correlation. Negative TCD studies do not rule out the presence of clinically significant vasospasm.

- In patients with acute neurologic deterioration attributable to ischemia from vasospasm, accepted empiric treatments include hemodynamic augmentation to increase blood pressure and endovascular rescue therapy such as intraarterial vasodilator infusion and cerebral angioplasty. Prophylactic use of these interventions is associated with increased complications and morbidity and is not recommended.

- To date, the only therapeutic agent with Class I evidence for decreasing the risk of poor outcome in SAH is nimodipine started within 96 hours of the initial hemorrhage and continued for 21 consecutive days.

- A common misconception is that nimodipine exerts therapeutic benefit through reducing cerebral vasospasm. In a randomized clinical trial, nimodipine use reduced delayed cerebral ischemia but had no impact on the rate of radiographic vasospasm.

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### Hyponatremia

Hyponatremia is common following SAH and can occur at different stages of the acute clinical course from different pathophysiologic processes. The two most common causes of hyponatremia following SAH are the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and cerebral salt wasting syndrome.[120] Accurate diagnosis of SIADH versus cerebral salt wasting is very important in critical care support of patients with SAH at risk for DCI, as these syndromes impact hemodynamic physiology differently and require divergent treatment approaches.

The two syndromes cannot be distinguished by laboratory features; both conditions have low serum sodium, high urine sodium, low serum osmolality, and high urine osmolality. The most important distinguishing feature between SIADH and cerebral salt wasting is the patient's intravascular volume status. Cerebral salt wasting can rapidly lead to clinically significant intravascular hypovolemia, whereas SIADH occurs in a euvolemic state. One possible distinguishing feature between cerebral salt wasting and SIADH is polyuria, which is often present with cerebral salt wasting. Without timely diagnosis and treatment, urinary loss of fluid and salt in cerebral salt wasting continues despite intravascular hypovolemia and can lead to or worsen brain ischemia and symptomatic DCI (**CASE 2-1B**). The focus in critical care management of cerebral salt wasting in SAH is to restore and maintain intravascular euvolemia with fluid resuscitation. Use of hypertonic solutions in cerebral salt wasting may not sufficiently correct intravascular hypovolemia even if it restores serum sodium to normal values. In some cases, cerebral salt wasting can present with very high urine output of more than 500 mL/h, making it difficult to maintain intravascular volume even with aggressive IV fluid resuscitation. Adding fludrocortisone (0.1 mg to 0.3 mg 2 times a day) is reasonable in clinically significant cerebral salt wasting. In a small randomized trial of cerebral salt wasting due to tuberculous meningitis, fludrocortisone use resulted in earlier normalization of serum sodium, although it did not impact outcome.[121] No randomized clinical trial data are available on fludrocortisone use in SAH. In patients with SAH with active cerebral salt wasting and high urine output, it is important to closely monitor and titrate treatment to intravascular volume status and serum sodium in real time.

As discussed earlier in this article, intravascular hypovolemia can significantly worsen brain injury and neurologic dysfunction in SAH, and an important principal in critical care support of patients with acute SAH at risk for DCI is to strictly maintain intravascular euvolemia. This can lead to the diagnostic challenge of distinguishing cerebral salt wasting from SIADH, as successful critical care support means the patient is never allowed to achieve a hypovolemic state. Although SIADH is typically treated with fluid restriction, this may not be an option in patients with SAH at high risk for DCI. The use of hypertonic fluid with high sodium content is a reasonable approach to correct moderate to severe hyponatremia while maintaining a euvolemic state in SAH patients with SIADH.

### Anemia

A large number of patients with SAH develop progressive anemia during their acute hospital course.[122,123] Given the concern that anemia may reduce oxygen-carrying capacity and oxygen delivery to the brain, particularly at high-risk periods such as during DCI, red blood cell transfusions have been



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studied in an attempt to reduce brain injury and improve SAH outcome. However, red blood cell transfusions may also have detrimental effects in SAH, such as further depletion of nitric oxide. Although small clinical trials suggested transfusion may be safe in SAH,[124] whether transfusion is beneficial in SAH and the optimal hemoglobin target are currently unknown.[123] SAHaRA (Aneurysmal Subarachnoid Hemorrhage—Red Blood Cell Transfusion and Outcome), a large multicenter randomized control trial comparing a liberal versus a restrictive red blood cell transfusion strategy in SAH, is ongoing.[125]

### Post–Subarachnoid Hemorrhage Headaches and Pain Control

More than 70% of all patients with aneurysmal SAH experience severe headaches that are at times refractory to multiple analgesic agents, including opioids.[126] Many patients report insufficient pain control following SAH, and a significant number continue to use opioids following hospital discharge. Chronic headaches may continue for more than a year after SAH.[127,128] Steroids are often used clinically as an adjunct therapy for SAH-associated headaches, although no high-level evidence is available for either efficacy or harm in this approach.[129] Novel narcotic-sparing approaches using pterygopalatine fossa or occipital nerve blockade have shown efficacy in small case series.[130,131] Larger clinical trials are needed to determine if these newer approaches effectively control SAH-associated headaches and reduce chronic narcotic use.

## PROGNOSIS AND LONG-TERM RECOVERY

Prognostication of SAH outcome is rapidly evolving over time, with many advances in surgical techniques, endovascular options, and critical care capabilities. Mortality from SAH has steadily decreased over past decades, although no randomized clinical trial has successfully identified a therapeutic agent that improves SAH outcome since the original nimodipine trial.[132] Whereas the original Hunt and Hess and World Federation of Neurological Surgeons studies found patients with grade 5 SAH almost uniformly had unfavorable outcomes, more modern studies from the past decade found that up to 39% of patients with grade 5 SAH can achieve favorable clinical outcome and good cognitive function.[133-136] Although high SAH clinical grade and older age remain important predictors for unfavorable long-term outcome in SAH, clinicians must be mindful of the time evolution and imprecision of current SAH prognostic tools, particularly in discussions regarding futility of care. Even patients with SAH with severe disability at hospital discharge can make significant gains with neurorehabilitation and achieve a moderate level of functional independence.[137-139] With the exception of patients who present with neurologic examinations concerning for imminent brain death, it is reasonable to offer state-of-the-art critical care resuscitation and support early in the acute course of SAH should this be consistent with the patient's values and wishes.

With the reduction in mortality and severe morbidity from SAH, more data are now emerging on long-term survivorship and the long-term impacts of SAH on patient-centered quality-of-life measures. Even in patients who achieve a favorable outcome as defined by a modified Rankin Scale of 2 or lower, significant numbers of survivors of SAH are unable to return to work and report subjective health impairment and chronic symptoms such as cognitive dysfunction, anxiety, depression, and, particularly, fatigue.[140-142] Unlike other patients with stroke, patients with SAH have good long-term physical

**KEY POINTS**

- No high-quality data support the use of fasudil, cilostazol, intrathecal fibrinolytics, and intrathecal vasodilators for delayed cerebral ischemia treatment or prevention in SAH.
- The use of hypervolemic, hypertensive, and hemodilutional (Triple H) therapy is associated with increased cardiopulmonary complications and is not recommended in modern neurocritical care for SAH.
- Intravascular hypovolemia is associated with delayed cerebral ischemia and unfavorable SAH outcomes and should be avoided. Guidelines recommend maintenance of normal intravascular volume in critical care support during the high-risk period for delayed cerebral ischemia.
- Up to 26% of patients with SAH may present with seizurelike symptoms at onset. Nonconvulsive seizures and nonconvulsive status epilepticus are seen in up to 18% of patients with SAH who are comatose, and they are associated with unfavorable outcome. Continuous EEG studies are recommended in patients with high clinical suspicion for seizures. Prolonged empiric anticonvulsant use, particularly phenytoin, is associated with less favorable outcome and neurocognitive dysfunction.
- Fever is common following SAH and is associated with higher SAH clinical severity and unfavorable outcome. Current guidelines recommend fever control in patients at higher risk of delayed cerebral ischemia.

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**KEY POINTS**

- **Hyponatremia is common following SAH and is most commonly caused by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or cerebral salt wasting syndrome. The correct diagnosis of SIADH versus cerebral salt wasting is very important as treatment approaches are divergent.**
- **Without timely diagnosis and treatment, cerebral salt wasting syndrome can rapidly lead to hypovolemia, worsen brain ischemia, and cause symptomatic delayed cerebral ischemia. Treatment of cerebral salt wasting should focus on restoring and maintaining intravascular euvolemia with fluid resuscitation.**
- **Although SIADH is typically treated with fluid restriction, this may not be an option in patients with SAH at high risk for delayed cerebral ischemia. Use of hypertonic fluid with high sodium content is a reasonable approach to correct moderate to severe hyponatremia while maintaining a euvolemic state in SAH patients with SIADH.**
- **A large number of patients with SAH develop progressive anemia. Whether transfusion is beneficial in SAH and the optimal hemoglobin target are currently unknown. A large multicenter randomized control trial comparing a liberal versus a restrictive red blood cell transfusion strategy in SAH is ongoing.**

function and independence in activities of daily living. Despite this, long-term disability impacting daily life is common even at 7 years post-SAH.[143] Few existing clinical trials have examined the potential impact of acute and subacute SAH treatment strategies on these long-term patient-centered outcome measures. Clinical studies on SAH survivorship are urgently needed to understand the burden of long-term disability and to explore strategies to improve quality of life in survivors of SAH.

## CONCLUSION

SAH is a neurologic emergency that tends to affect patients who are younger and female, and it continues to cause significant mortality and long-term morbidity. In addition to having a life-threatening initial presentation requiring urgent transfer to centers equipped to provide emergent surgical, endovascular, and critical care interventions, patients with SAH develop multiorgan dysfunctions requiring prolonged neurocritical care support in high-volume centers. Although no new single drug or intervention has demonstrated efficacy in improving SAH outcome, mortality and morbidity from SAH have steadily improved over time, and favorable outcome is possible even in patients initially presenting with severe clinical grade SAH. Keys to optimizing good outcome in SAH include the following:

- **Timely and accurate initial recognition and diagnosis of SAH**
- **Expeditious acute resuscitation and stabilization of life-threatening organ dysfunctions and timely obliteration of the bleeding aneurysm to avoid rebleeding**
- **Minimizing additional brain injury with close monitoring and high-quality neurocritical care support through the high-risk period for DCI**
- **Timely recognition, correct diagnosis, and guideline-driven treatment of multiorgan dysfunctions to optimize protection of the injured brain**
- **Neurorehabilitation and future studies on long-term follow-up care to reduce the burden of long-term disability on SAH survivors**

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